RATIONAL ANTIRETROVIRAL DRUG USE IN PREGNANT AND POSTPARTUM WOMEN LIVING WITH HIV

By

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ABSTRACT

Effective antiretroviral therapy is critical during pregnancy for women living with HIV (WLHIV) for the health of both the mother and the fetus, but there are knowledge gaps in the pharmacology of new HIV drugs, physiologic changes affecting drug disposition, and safety in pregnancy that prevent efficient and effective deployment of our most promising new HIV drugs in pregnant women. The objective of this thesis is to advance our knowledge of the pharmacology and safety of several HIV drugs – darunavir (DRV)/ritonavir (RTV), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF)--in pregnant and post-partum women, using tools such as non-compartmental pharmacokinetic analytic and pharmacometric (population pharmacokinetic modeling) approaches. Research goals include describing DRV, RTV and TDF pharmacokinetics (PK) in pregnancy, identifying predictive covariates for tenofovir disposition in pregnant women using TDF, and understanding the safety and efficacy of TDF and TAF use in pregnant WLHIV, with the overall goal of optimizing HIV therapeutics for pregnant WLHIV.

The five-parts of this thesis are as follows: 1) Chapter 1 introduces HIV in pregnancy using data from the Pediatric AIDS Clinical Trials Group (PACTG 076), the first randomized clinical trial of zidovudine versus placebo during pregnancy, and then discussed physiologic changes during pregnancy that affect drug disposition; current state of research involving pregnant women; implications of excluding pregnant women from drug trials using cobicistat as an example; and ethical issues surrounding pharmacologic studies involving pregnant women. 2) Chapter 2 discussed findings from a non-compartmental PK study of darunavir-boosted-ritonavir; 3) Chapter 3 examined a population-PK study of tenofovir in pregnant and postpartum women living with HIV using TDF; 4) Chapter 4 explored the pharmacoepidemiology of TDF when compared to

TAF in pregnant women living with HIV; 5) and Chapter 5 concludes this thesis. The major research questions of chapters 2 and 3 focus on understanding the effects of the physiologic changes during pregnancy on drug PK, and patient-specific factors that account for variability in drug disposition. Chapter 4 focuses on understanding the safety and efficacy of TDF and TAF use in pregnant women living with HIV and their fetuses.

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PREFACE

"The person who takes medicine must first recover twice, once from the disease and once from the medicine."

--Sir William Osler

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DEDICATION

To my beloved wife, Uzoamaka Akudo Eke, MD, and my three lovely daughters – Adaugo Chikasi Eke, Akachi Chizurum Eke, and Amarachi Oluoma Eke. Finally, To my Lord God Almighty for granting me the grace to live, breath, and work hard. Success is the sum of many achievements and failure is an invaluable opportunity to improve.

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CHAPTER 1: INTRODUCTION

The use of antiretroviral (ARV) medications in pregnant women living with human immunodeficiency virus (HIV) continues to be of critical public health importance.[1,2] Without treatment, about 15-40% of pregnant women living with HIV are at risk of transmitting the virus to their fetuses.[3] The 1994 landmark Pediatric AIDS Clinical Trials Group (PACTG) 076 study, the first study of antiretroviral safety and efficacy in pregnancy, showed that the administration of zidovudine (ZDV) to pregnant women living with HIV and to their neonates after birth, decreased the risk of perinatal HIV transmission by 68% (from 25.5% to 8.3%).[4] Since 1994, combination ARV therapies with multiple potent HIV drugs have proven to be more effective than ZDV alone at preventing perinatal HIV transmission, changing the trajectory for the treatment of HIV during pregnancy and reducing perinatal transmission rates to negligible numbers, while improving maternal health immensely.

The World Health Organization (WHO),[5] United States Department of Health and Human Services (DHHS)[1] and the European AIDS Clinical Society (EACS)[6] HIV perinatal guidelines all recommend that pregnant women living with HIV receive a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) with a third ARV from another class. Currently recommended regimens for most pregnant women include two NRTI backbones of abacavir/lamivudine, tenofovir disoproxil fumarate (TDF)/lamivudine or TDF/emtricitabine, plus an integrase strand inhibitor (raltegravir or dolutegravir) or a boosted protease inhibitor (darunavir/ritonavir or atazanavir/ritonavir).[1] Cobicistat-boosted fixed drug combinations (darunavir-cobicistat, elvitegravir-cobicistat, and atazanavir-cobicistat) were classified as preferred ARVs during pregnancy, but in November 2018, the FDA revised drug labeling for cobicistat containing ARVs

that recommended against use of cobicistat fixed-dose combinations in pregnancy. This was made several years after these cobicistat-containing regimens were first approved for use in adults in the United States.[7,8] The persistent gap between initial licensure of drugs and availability of pertinent pregnancy-specific pharmacokinetic and safety information has remained a long-standing failure of standard drug development programs. Pregnancy-specific pharmacokinetic and pharmacodynamic information is not required for approval of most new drugs, and drug development programs in the United States routinely exclude pregnant women in their phase II and III protocols. Consequently, these cobicistat-containing fixed-dose combinations, which provide favorable and well-tolerated alternatives to ritonavir containing antiretroviral regimens in non-pregnant adults, were widely prescribed to pregnant women with HIV for over 6 years before pregnancy-specific pharmacokinetic data describing the dangerously reduced drug concentrations during the second and third trimesters of pregnancy became available. The cobicistat-pregnancy experience has provided two key lessons: first, because boosters (pharmacoenhancers) act on different drugs via different mechanisms, the physiologic changes of pregnancy may alter the boosting effect on some drugs but not others (as cobicistat boosting differed based on the antiretroviral drug class); and second, it emphasized the need to continue to find innovative ways to study drug disposition in pregnant women.[9]

The physiologic changes during pregnancy may alter the boosting effect on some drugs but not others. Pregnancy is associated with several structural and functional changes that influence the processes of drug absorption, distribution, metabolism, and excretion [10]. For example, there is increased drug transit time in the gastro-intestinal tract, increased volume of distribution of drugs, increased creatinine clearance, and increased metabolism of most medications during pregnancy.

Pregnancy is associated with about 40-50% rise in blood volume, reaching a peak at approximately 32 weeks of gestation.[11] In addition, there is maternal weight gain and increased body fat (a mean increase of 12-20 kg) from baseline during the course of pregnancy.[12] The pharmacokinetic consequence of increased maternal blood volume and increased fat and body mass during pregnancy is that hydrophilic drugs tend to be relatively minimally distributed (low volume of distribution), while lipophilic drugs tend to have a large volume of distribution, particularly into fatty tissues during pregnancy compared to the non-pregnant state. These physiologic changes may result in increased loading and maintenance medication dosage requirements, as well as the potential for sub-therapeutic drug dosing during pregnancy.

Renal blood flow rises to about 70-80% from its baseline value at 20-22 weeks of gestation, peaks around 32-24 weeks of gestation, and then falls to about 60-70% above pre-pregnancy levels towards the end of pregnancy, while the glomerular filtration rate (GFR) rises in parallel to about 40-50% of its baseline values at 20-22 weeks, then continues to increase through most of the 3rd trimester, upto 36-38 weeks of gestation, when it declines steadily until the time of delivery.[13,14] A 2019 systematic review of serum creatinine concentrations during pregnancy from 49 studies that measured over 4,000 serum creatinine concentrations in healthy pregnant women demonstrated that the mean values for serum creatinine in the 1st, 2nd and 3rd trimesters were 16%, 23% and 20% lower when compared to baseline values in non-pregnant adults.[15] The increased renal blood flow and increased glomerular hyper-filtration are responsible for the increased creatinine clearance, decreased blood urea nitrogen levels, and increased protein excretion (up to 300mg/day) during pregnancy.[16]

It is crucial to note that while it is important to understand the impact individual organ-system changes can have on drug disposition during pregnancy, the final plasma drug concentration during pregnancy depends on a complex relationship (net effect) between many PK variables, including the fraction of drug absorbed, the physicochemical properties governing diffusion across membranes, drug bioavailability, protein binding and unbound fractions of drug, volume of distribution, intrinsic organ clearance, organ extraction ratio (hepatic or renal), and several other PK variables. For example, darunavir (a protease inhibitor) is approximately 85% bound to plasma-proteins, but plasma proteins tend to decrease during pregnancy, so the bound fraction of darunavir is expected to decrease. Darunavir has a low hepatic extraction ratio (< 0.3), is metabolized extensively by cytochrome P450-3A (which increases in pregnancy), and eliminated (>90%) by the liver through hepatic clearance.[17] During pregnancy, darunavir protein binding decreases to approximately 30% (compared to pre-pregnancy), while the free-fraction (active drug) would be expected to increase. Thus, the increases in darunavir hepatic drug metabolism, volume of distribution, and clearance during pregnancy, and the net sum of these changes, have major consequences for low darunavir plasma concentrations during pregnancy.[18-23]

Understandably, ethical issues exist regarding pharmacologic research in pregnant women. One of the reasons that pregnant women have been systematically excluded from research is their perceived status as 'vulnerable'. This ethical complexity stems out of the need to balance the maternal and fetal risks versus benefits during pregnancy. Maternal and fetal interests usually align, as appropriate care of the woman is necessary for the health of the fetus, but these interests may diverge in the setting of clinical pharmacology studies in pregnant women, especially research that is not focused on concerns of pregnancy or fetal health. However, remarkable efforts by the

National Institutes of Health (NIH) in the early 1990s led to a significant increase in the percentage of women participating in research trials.[24] As a result, a great amount of pertinent information was obtained describing diseases and their treatment as they relate to women - information that was previously unavailable. Although significant changes in research methodology and practice have caused an increase in the number of pregnant women involved in pharmacologic research, knowledge gaps still remain. While these challenges persist, it is worthy to note that there has been a renewed government interest in increasing pharmacologic studies during pregnancy through the Task Force on Research Specific to Pregnant and Lactating Women (PRGLAC), established as part of the 21st Century Cures Act.[25] Continued emphasis on recruitment of pregnant women into clinical pharmacology studies must be encouraged.

The remaining chapters of this thesis are as follows: Chapter 2 discusses the findings from a non-compartmental pharmacokinetic study of darunavir-boosted-ritonavir; Chapter 3 examined a population-PK study of tenofovir in pregnant and postpartum women living with HIV using TDF; Chapter 4 explored the pharmacoepidemiology of TDF use when compared to TAF use in pregnant women living with HIV; and Chapter 5 concludes this thesis. The major research questions of chapters 2 and 3 focus on understanding the effects of the physiologic changes during pregnancy on drug PK, and patient-specific factors that account for variability in drug disposition. Chapter 4 focuses on understanding the safety and efficacy of TDF and TAF use in pregnant women living with HIV and their fetuses. These lay the groundwork for ongoing studies that will endeavor rational and effective drug use in pregnant women living with HIV (chapter 5).

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CHAPTER 2

Darunavir Pharmacokinetics with an increased dose during pregnancy.

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ABSTRACT:

Background: This study aims to evaluate the pharmacokinetics of an increased dose of darunavir (800 mg twice daily) with 100 mg ritonavir during pregnancy and postpartum.

Methods: Darunavir (DRV) and ritonavir (RTV; r) intensive pharmacokinetic evaluations were performed at steady state during the second and third trimesters of pregnancy (DRV/r 800/100 mg bid) and 2-3 weeks postpartum (DRV/r 600/100 mg twice daily). Plasma concentrations of darunavir and ritonavir were measured using high-performance liquid chromatography (HPLC). Target darunavir area under the concentration time curve (AUC) was >70% (43.6 mcg*hr/mL) of median AUC (62.3 mcg*hr/mL) in non-pregnant adults on twice daily darunavir-ritonavir 600/100 mg.

Results: Twenty-four women were included in the analysis. Darunavir AUC_{0-12} was lower with the increased dose during the second [(geometric mean ratio (GMR) of 0.62 (IQR 0.44-0.88; p=0.055)] and third trimesters (GMR 0.64 (IQR 0.55-0.73; p=<0.001) compared to postpartum. Darunavir apparent clearance was higher in during the second (GMR 1.77 (IQR 1.24-2.51; p=0.039) and third trimesters (GMR 2.01 (IQR 1.17-2.35; p=<0.001) compared to postpartum. Similarly, ritonavir AUC_{0-12} was lower during the third trimester (GMR 0.65 (IQR 0.52-0.82; p=0.007) compared to postpartum, while its apparent clearance was higher during the third trimester (GMR 1.53 (IQR 1.22-1.92; p=0.008) compared to postpartum. No major drug-related safety concerns were noted.

Conclusion: Increasing darunavir dose to 800 mg BID failed to significantly increase darunavir exposure compared to 600 mg BID. Other strategies, such as increasing the ritonavir dose should be investigated.

INTRODUCTION:

Darunavir (DRV), in combination with low-dose ritonavir, is one of the two protease inhibitors (PIs) currently recommended by the US Perinatal Guidelines Panel for use in pregnant women living with HIV for treatment of HIV infection and for prevention of perinatal transmission.[1] In most countries, darunavir is available as 600 mg and 800 mg tablets, and dosed as darunavir/ritonavir (DRV/RTV) 800mg/100 mg daily for darunavir naïve patients and 600mg/100mg twice daily for treatment of antiretroviral experienced patients. Due to physiological changes that occur during pregnancy, there is decreased exposure to many protease inhibitors during the 3rd trimester of pregnancy.[2,3]

The clinical relevance of these changes during pregnancy were described in prior PK studies of DRV/RTV during pregnancy and postpartum.[4-7] In PK studies of 600mg/100mg DRV/RTV twice daily and 800mg/100mg once daily DRV/RTV, darunavir and ritonavir exposures (area under the concentration time curve and plasma trough concentrations) were lower during the third trimester of pregnancy compared to postpartum.[4-7] For pregnant women living with HIV, these lower antiretroviral drug exposures during pregnancy can increase the risk of maternal viremia, and, in turn, increase the potential for drug resistance and perinatal transmission.[8] Although plasma concentrations of RTV boosted DRV were lower during pregnancy compared to postpartum in these prior studies, the reduced DRV concentrations were still above the exposures needed for viral suppression.

Examining known pharmacokinetic-pharmacodynamic (PKPD) relationships of darunavir (AUC, viral response and protein-adjusted IC_{50}/IC_{90}) in the context of lower exposures and what a clinically relevant decrease means in relation to these targets is critical during pregnancy. Three darunavir/ritonavir randomized clinical trials - POWER I,[9] POWER II[10] and POWER III[11]

demonstrated a dose-response relationship between darunavir plasma trough concentrations (C_{min}) and HIV antiviral response.[12,13] However, this PKPD relationship between C_{min} and viral response were not observed in two other darunavir randomized clinical trials - ODIN[14] and ARTEMIS.[15,16] Hence, darunavir exposure-response data from these five trials were not sufficient to recommend a minimum trough concentration.[17] Therefore, darunavir C_{min} might not be the most appropriate PK parameter to evaluate DRV/RTV antiviral response. The established darunavir EC_{50} for wild-type virus and resistant-type virus are 0.055 μg/mL[17,18] and 0.55 μg/mL respectively,[19] while darunavir EC_{90} for wide type virus is 0.2. These parameters are frequently used for monitoring response of darunavir in both treatment naïve and treatment experienced patients in pregnant and non-pregnant adults.

Due to low darunavir/ritonavir concentrations with 800 mg once-daily dosing of darunavir in these studies, only the 600 mg twice-daily dosing is currently recommended by the US Perinatal Guidelines Panel for use in pregnancy.[1] The objective of the current study was to evaluate the hypothesis that an increased dose darunavir (800/100 twice daily) during pregnancy would increase darunavir plasma exposure to levels similar to those seen in non-pregnant women.

METHODS:

The study protocol, the informed consent documents, and all subsequent modifications were reviewed and approved by the local institutional review board (IRB)/Ethics Committee responsible for oversight of the study, including the Johns Hopkins University IRB. The study followed all relevant human subject research guidelines. All participants provided signed informed consent before participation.

Pregnant women living with HIV were eligible for enrollment in the second and third trimesters if they were receiving darunavir as part of clinical care according to the following dosing schedule: darunavir/ritonavir 800/100 mg twice daily during pregnancy and decreased to darunavir/ritonavir 600/100 mg twice daily within a week after delivery, and postpartum PK was performed up to 6 weeks after delivery. All antiretroviral medications were prescribed by the participants' clinical care providers and dispensed by local pharmacies, as per local standard of care. Maternal exclusion criteria were current use of medications known to interfere with darunavir metabolism (including amiodarone, atazanavir and boceprevir), presence of hemophilia, liver disease, hyperlipidemia, phenylketonuria, and other clinical or laboratory toxicity that, per site investigators, would require a change in the antiretroviral regimen. Mothers and their infants continued in the study for safety evaluations until 6 months after delivery. Infant HIV status was evaluated during the first 6 months of life by standard laboratory tests. To be definitively diagnosed as uninfected, an infant needed to have at least two negative HIV nucleic acid tests with one after 1 month and the other after 4 months of age. Infants were classified as indeterminate if their available HIV nucleic acid test results were negative but did not include 2 negative tests with one after 1 month and another after 4 months of age.

Clinical and laboratory data:

Maternal demographic and clinical information were abstracted from the medical record, including maternal HIV-1 RNA, CD4+ lymphocyte count, maternal age, ethnicity, weight and concomitant medications. Plasma HIV-1 RNA assays were performed locally. Study mothers and infants were followed through six months after delivery. Neonatal gestational age at the time of delivery, birth weight and HIV infection status data were collected from the infant's medical record. Physical

examinations were performed on neonates after delivery, and infant laboratory evaluations were performed as clinically indicated, and darunavir wash-out pharmacokinetic sampling was performed on the neonates. Maternal clinical and laboratory toxicities were assessed through clinical and laboratory evaluations on each pharmacokinetic sampling day, at delivery, and at 24 weeks postpartum. Any additional toxicities noted as part of clinical care were also recorded. The study team reviewed toxicity reports on monthly conference calls, although each participant's physician was responsible for toxicity management. The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.0, dated November 2014, was used to grade adverse events for study participants.[20] All toxicities were followed through resolution or 24 weeks postpartum.

Sample collection and drug assays:

Plasma darunavir and ritonavir samples for intensive PK sampling were drawn immediately prior to an observed dose and at 1, 2, 4, 6, 8, and 12 hours post-dose. Samples were collected at 20-26 weeks gestation for 2nd trimester PK evaluation; at 30-36 weeks gestation for 3rd trimester PK evaluation and between the time of delivery up to 6 weeks after delivery for postpartum evaluation. Paired maternal and cord blood samples were collected at delivery and infant washout PK samples were collected at 2-10, 18-28, 36-72 hours after birth, and at 5-9 days of life. Plasma darunavir and ritonavir concentrations were determined by high-performance liquid chromatography (HPLC) with ultraviolet detection at the University of California, San Diego Pediatric Pharmacology Laboratory. Briefly, plasma proteins were precipitated using acetonitrile (ACN) and supernatant injected directly onto a LUNA C-18 reversed phase HPLC column (Phenomenex Inc., Torrance, CA, USA). Drugs were separated isocratically using a mobile phase consisting of

10mM potassium phosphate buffer pH 4.2: ACN (62:38 v/v). The flow rate was 1.2 mL/min and ultraviolet (UV) detection was at 206 nm. The detection limit for both darunavir and ritonavir was 0.09mcg/mL (1/2 limit = 0.045 mcg/mL). The mean inter and intra-assay coefficients of variation based on validation data (quality control samples run at multiple concentrations over the range of 0.092–20 ug/mL) were 5.1% and 3.8%, respectively. Darunavir and ritonavir were stable in plasma stored at -20°C. Darunavir and ritonavir were stable in plasma for over 60 days (long-term stability) at -20C, and plasma samples of both darunavir and ritonavir were stable over at least six freeze/thaw cycles. Concentrations below the detection limit were treated as half this limit for analysis.

Pharmacokinetic and statistical analysis:

Darunavir and ritonavir plasma concentrations were analyzed using standard descriptive statistics and are presented as medians with interquartile ranges. Areas under the concentration time curve (AUC) for plasma from pre-dose concentration (C_0) to 12 hours post dose (AUC_{0-12}) were estimated using the trapezoidal rule, with apparent clearance as dose/AUC_{0-12}. Target darunavir AUC was >70% (43.6 mcg*hr/mL) of median AUC (62.3 mcg*hr/mL) in non-pregnant adults on darunavir-ritonavir 600/100 mg twice daily. The P1026s protocol has an early stopping provision allowing an arm to be closed at any time after a minimum of 12 participants have been enrolled in an arm if six or more pregnant women fail to meet the PK exposure target for that arm.[21] PK parameters were calculated with standard non-compartmental methods. Within-participant comparisons (second or third trimester versus postpartum) were performed for continuous outcome measures using the Wilcoxon signed-rank test and for dichotomous outcome measures using McNemar's test. Between-participant comparisons were performed for continuous outcome

measures using the Wilcoxon rank-sum test and for dichotomous outcome measures using the chi-square or Fisher exact test. A two-sided p-value <0.1 was considered statistically significant. 90% confidence limits for the geometric mean of the within-person ratios of the PK exposure parameters were calculated to describe the range of values that were consistent with the observed data, to assess whether there was a clinically important difference in exposure. Data analysis was done using WinNonlin (version 7.0; Pharsight Corporation, Mountain View, CA, USA) and SAS (version 9.4, SAS Institute, Cary NC).

RESULTS:

Demographic characteristics and clinical outcomes for the 24 study mother-infant pairs are shown in ***Table IIa***. Plasma concentration data were available for 9 (37.5%) women in the second trimester, 24 (100%) women in the third trimester, and 24 (100%) postpartum. The median age of the mothers participating in this study was 26.9 years (IQR 21.4 to 34.4). Twelve (50%) of the 24 mothers were black, eleven were Hispanic (46%) and one (4%) was Asian. The median gestational age at the time of sampling was 23.9 weeks (IQR: 23.1 to 24.7) in the 2nd trimester, 33.5 weeks (32.5 to 34.4 weeks) in the 3rd trimester, and median postpartum sampling time was 2.8 weeks after delivery (IQR: 2 to 3 weeks postpartum), ***Table IIa***. Six women (66.7 %) had plasma HIV-1 RNA $\leq$50 copies/mL during the second trimester, 21 women (87.5%) had plasma HIV-1 RNA $\leq$50 copies/mL during the third trimester, 20 women (80%) had plasma HIV-1 RNA $\leq$50 at delivery, and 17 women (70.8%) had plasma HIV-1 RNA $\leq$50 copies/mL in the postpartum period. The median CD4 count (cells/mL) was 682 (IQR, 300-761) in the second trimester, 538 (303-911) in the 3rd trimester, and 653 (IQR 395-911) postpartum. The median gestational age at delivery was 39.0 weeks (range 38.1-39.6), with an average birth weight of 3118 grams (range 2770 to 3405).

Table IIa: Increased dose darunavir/ritonavir subjects: demographic characteristics and outcomes (n=24).

Maternal characteristics	N(%) or median (IQR)
Age at delivery (years)	26.9 (21.4, 34.4)
Weight at delivery (kg)	86.2 (68.4, 95.7)
Race/Ethnicity	
Asian, Pacific Islander	1 (4%)
Black Non-Hispanic	12 (50%)
Hispanic (Regardless of Race)	11 (46%)
Duration of darunavir before PK evaluations (weeks)	
Before 2nd trimester PK evaluations	149 (64.9, 262.1)
Before 3rd trimester PK evaluations	102.1 (26.0, 190.4)
Number of mothers taking concomitant ARVS at the time of 3rd pharmacokinetic evaluations	*FTC 15; TDF 15; ZDV 4; 3TC 3; RAL 5; RPV 2; DTG 3; ATV 2; ENF 1.
Second trimester	
Gestational age (weeks)	23.9 (23.1, 24.7)
Number of mothers with viral load ≤50 copies/mL	6 (66.7%)
CD4 (cells/mm^3)	682 (300, 761)
Third trimester	
Gestational age (weeks)	33.5 (32.5, 34.4)
Number of mothers with viral load ≤50 copies/mL	21 (87.5%)
CD4 (cells/mm^3)	537.5 (303, 910.5)
Delivery	
Number of mothers with viral load ≤50 copies/mL	20 (80%)
CD4 (cells/mm^3)	506 (338, 786)
Postpartum	
Weeks post-delivery (weeks)	2.8 (2.4, 3.2)
Number of mothers with viral load ≤50 copies/mL	17 (70.8%)
CD4 (cells/mm^3)	652.5 (395, 910.5)
Pregnancy outcomes	
Gestational age (weeks)	39 (38.1, 39.6)
Birth weight (grams)	3118 (2770, 3405)
Infection status	20 uninfected/4 indeterminate

**ARVs (Antiretrovirals), FTC (emtricitabine), TDF (tenofovir disoproxil fumarate), ZDV (zidovudine), 3TC (lamivudine), RAL (raltegravir), RPV (rilpivirine), ATV (atazanavir); ENF (enfuvirtide) and DTG (dolutegravir). Interquartile ranges (IQR) are in brackets.*

Darunavir pharmacokinetic data are shown in ***Table IIb***. Darunavir AUC_{0-12} was lower in the 2nd trimester (geometric mean ratio, GMR 0.62 (CI 0.44-0.88; p=0.055) and 3rd trimester (GMR 0.64 (CI 0.55-0.73; p<0.001) compared to postpartum. Darunavir apparent clearance (CL/F) was higher

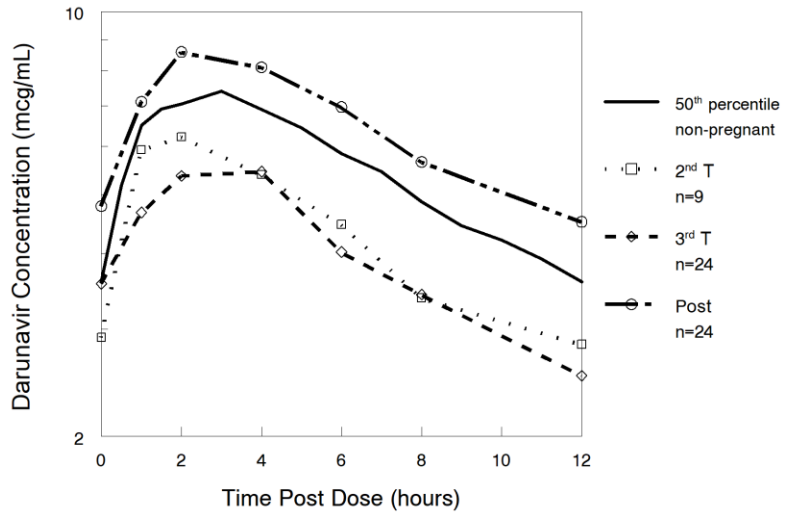
in the 2nd trimester (GMR 1.77 (CI 1.24-2.51; p=0.039) and 3rd trimester (GMR 2.01 (IQR 1.17-2.35) compared to postpartum (P<0.001). Darunavir maximum plasma concentration (C_{max}) [(GMR 0.71 (CI 0.62-0.81); p<0.001) and the last observed quantifiable darunavir concentration (C_{last}) [(GMR 0.59 (CI 0.50-0.69); p<0.001) were lower in the 3rd trimester compared to postpartum. Darunavir apparent volume of distribution (V/F) was higher in the second trimester [(GMR 1.58 (CI 1.23-2.04); p=0.016)] and third trimester [(GMR 2.01 (CI 1.53-2.65); p<0.001)] compared to postpartum. ***Figures IIa-d*** show median darunavir concentrations (***IIa***); darunavir area under the curve (***IIb***); darunavir apparent clearance (***IIc***); and darunavir maximum concentration (***IId***) in the 2nd trimester, 3rd trimester and postpartum respectively.

<u>Table IIb:</u> Darunavir pharmacokinetics comparison of 2nd trimester (N=9) versus postpartum (N=24); and 3rd trimester (N=24) versus postpartum (N=24)

PK Parameter	#Second trimester (2T); (n=9)	#Third trimester (3T); (n=24)	#Postpartum (PP); (n=24)	Geometric mean Ratio, GMR (90% CI); 2T/PP, n=8	p-value	Geometric mean Ratio, GMR (90% CI); 3T/PP, n=23	p-value
DRV AUC_{0-12} (µg*hr/mL)	55.1 (46.4, 57.7)	51.8 (41.2, 57.7)	79.6 (66.6, 103.0)	0.62 [0.44, 0.88]	**0.055**	0.64 [0.55, 0.73]	**<0.001**
DRV CL/F (L/hr)	14.2 (12.3, 15.6)	15.6 (13.9, 19.4)	7.72 (6.19, 10.32)	1.77 [1.24, 2.51]	**0.039**	2.01 [1.17, 2.35]	**<0.001**
DRV V/F (Liters)	152.7 (137.0, 259.2,	174.6 (143.3, 233.7)	101.2 (62.1, 133.6)	1.58 [1.23, 2.04]	**0.016**	2.01 [1.53, 2.65]	**<0.001**
DRV $T_{1/2}$ (hours)	7.95 (6.21, 9.82)	7.65 (6.57, 9.04)	8.66 (6.72, 10.38)	0.90 [0.74, 1.08]	0.313	1.01 [0.83, 1.22]	0.637
DRV C_{min} (µg/mL)	2.84 (1.21, 3.23)	2.39 (1.72, 2.82)	1.12 (0.52, 5.01)	2.52 [0.68, 9.35]	0.578	0.90 [0.52, 1.58]	**0.011**
DRV C_{last} (µg/mL)	2.84 (2.24, 3.23)	2.52 (2.06, 2.90)	4.51 (3.72, 5.28)	0.66 [0.39, 1.12]	0.109	0.59 [0.50, 0.69]	**<0.001**
DRV C_{max} (µg/mL)	6.22 (5.30, 8.42)	6.55 (5.38, 7.43)	8.96 (7.93, 10.85)	0.81 [0.64, 1.01]	0.148	0.71 [0.62, 0.81]	**<0.001**
DRV C_0 (µg/mL)	2.91 (1.55, 5.61)	3.57 (2.79, 4.09)	3.56 (2.14, 6.42)	2.97 [0.75, 11.8]	0.469	1.00 [0.56, 1.81]	**0.045**
DRV C_{12} (µg/mL)	2.84 (2.24, 3.23)	2.52 (2.06, 2.91)	4.51 (3.72, 5.30)	0.66 [0.39, 1.12]	0.109	0.58 [0.49, 0.69]	**<0.001**

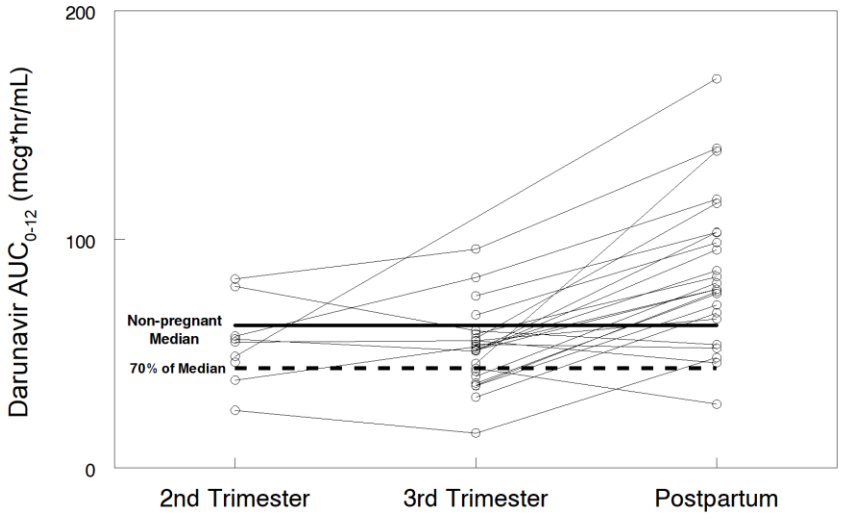
*p-value for Wilcoxon rank-sum test; AUC_{0-12} = area under concentration (AUC) vs time curve (0 to 12 hours post-dose), Cl/F = apparent oral clearance, V/F = apparent volume of distribution; $T_{1/2}$ = elimination half-life; C_{last} = last observed quantifiable concentration; C_0 = initial concentration at time zero; C_{12} = concentration at 12 hours post-dose; C_{min}= minimum concentration, C_{max}= maximum concentration; CI = confidence interval.
#Values are medians (interquartile ranges).

<u>Figure IIa:</u> Median darunavir plasma concentrations.

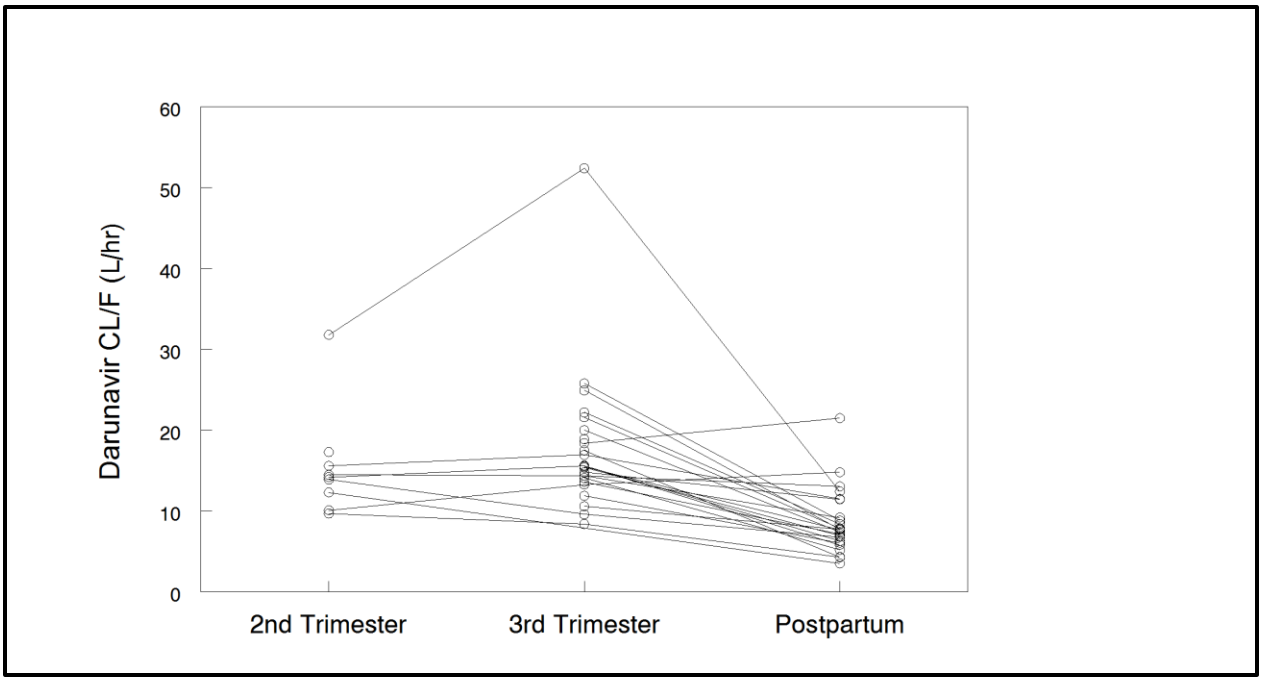


The 50th percentile data in this figure represents DRV/RTV 600 mg/100 mg BID in non-pregnant adults.

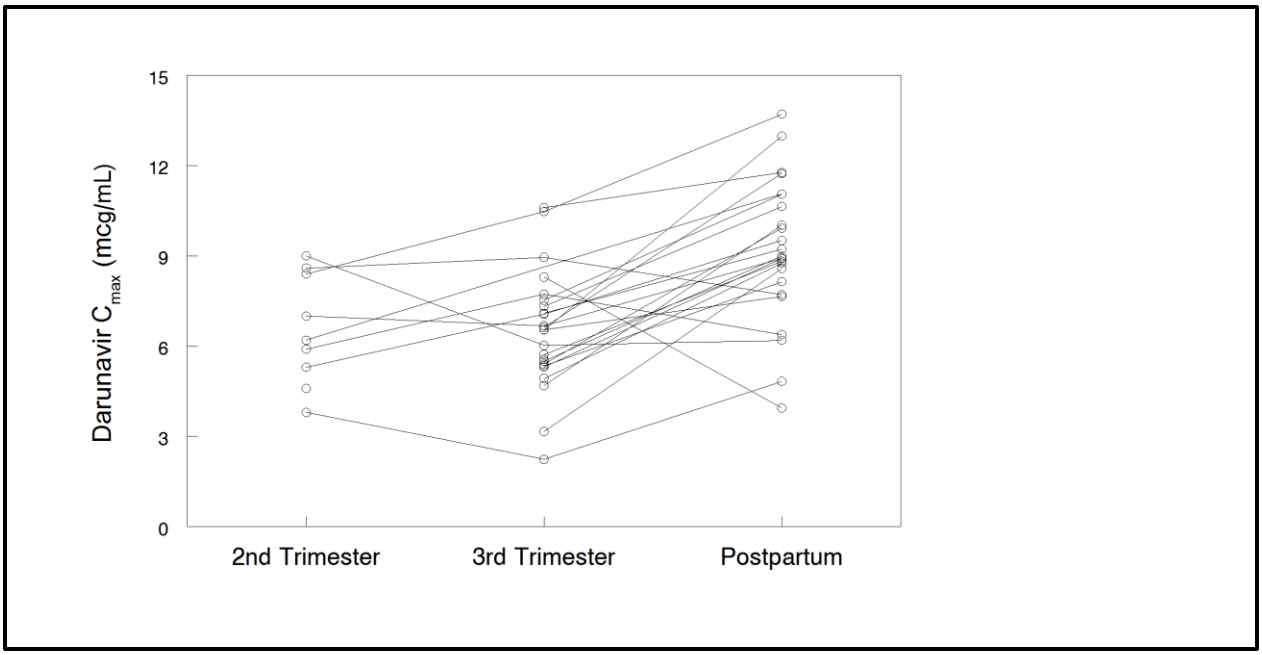
<u>Figure IIb</u> – Darunavir area under the curve (AUC_{0-12}).



<u>Figure IIc</u>: Darunavir apparent clearance (CL/F).



<u>Figure IId:</u> Darunavir maximum plasma concentration - C_{max}.



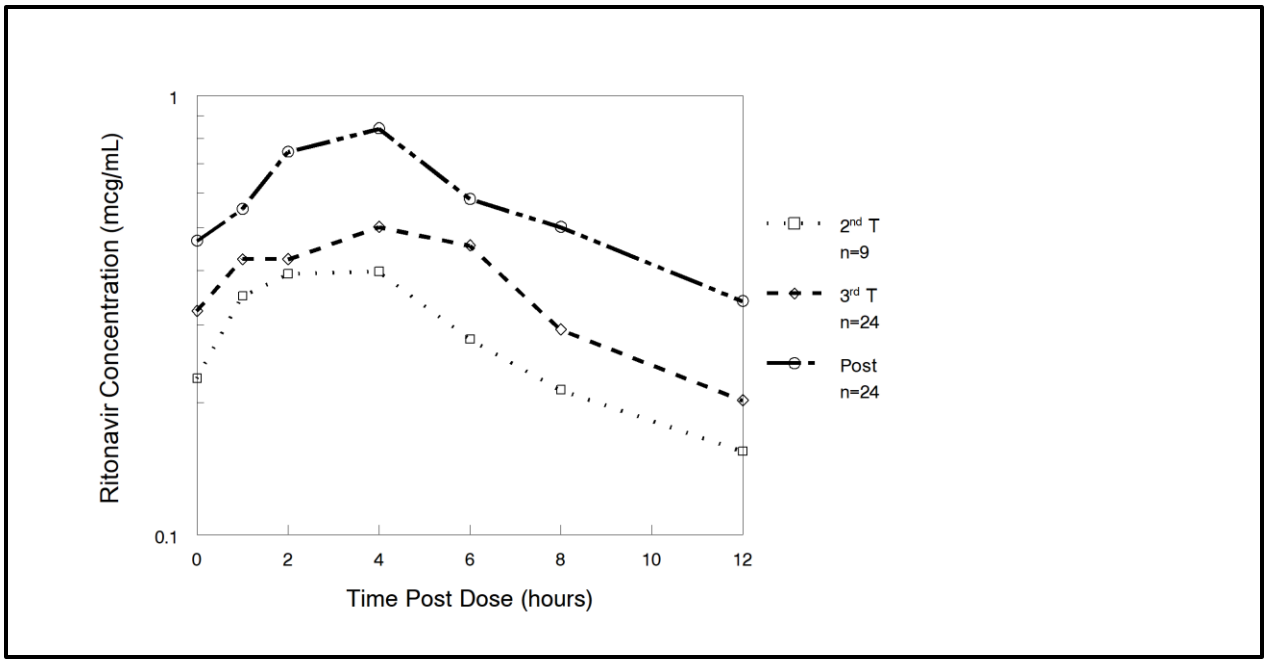
Ritonavir pharmacokinetic data are shown in ***Table IIc***. Ritonavir AUC_{0-12} was lower in the 3rd trimester (geometric mean ratio 0.65 (CI 0.52-0.82; p=0.007) compared to postpartum. Ritonavir apparent clearance (CL/F) was higher in the 3rd trimester (geometric mean ratio 1.53 (CI 1.22-1.92; p=0.008) compared to postpartum. Ritonavir last observed quantifiable concentration (C_{last}) [(geometric mean ratio 0.64 (CI 0.40-1.04); p=0.065)] and maximum serum concentration (C_{max}) [(geometric mean ratio 0.67 (CI 0.54-0.83); p=0.004)] were lower in the 3rd trimester compared to postpartum. Ritonavir apparent volume of distribution (V/F) was higher in the second trimester [(GMR 2.12 (CI 1.42-3.16); p=0.012)] compared to postpartum. ***Figure IIe*** shows mean ritonavir concentrations in the 2nd trimester, 3rd trimester and postpartum.

Table IIc: Ritonavir pharmacokinetics comparison of 2nd trimester (N=9) versus postpartum (N=24); and 3rd Trimester (N=24) versus postpartum (N=24)

PK Parameter	#Second trimester (2T); (n=9)	#Third trimester (3T); (n=24)	#Postpartum (PP); (n=24)	Geometric mean Ratio, GMR (90% CI); 2T/PP, n=8	p-value	Geometric mean Ratio, GMR (90% CI); 3T/PP, n=23	p-value
RTV AUC_{0-12} (µg*hr/mL)	3.19 (2.67, 6.10)	4.83 (3.23, 7.00)	6.68 (5.07, 11.2)	0.88 [0.61, 1.27]	0.547	0.65 [0.52, 0.82]	**0.007**
RTV CL/F (L/hr)	14.2 (12.3, 15.6)	15.6 (13.9, 19.4)	7.72 (6.20, 10.3)	1.14 [0.79, 1.64]	0.383	1.53 [1.22, 1.92]	**0.008**
RTV V/F (Liters)	245.0 (194.4, 389.3)	210.7 (131.0, 328.9)	89.6 (48.3, 163.5)	1.41 [0.73, 2.72]	0.547	2.12 [1.42, 3.16]	**0.012**
RTV $T_{1/2}$ (hours)	7.21 (5.16, 17.5)	6.51 (3.67, 12.33)	4.73 (3.85, 6.35)	1.24 [0.78, 1.97]	0.383	1.50 [0.95, 2.37]	0.226
RTV C_{min} (µg/mL)	0.12 (0.05, 0.34)	0.20 (0.08, 0.29)	0.29 (0.05, 0.44)	1.26 [0.76, 2.11]	0.313	0.90 [0.48, 1.69]	0.164
RTV C_{last} (µg/mL)	0.16 (0.12, 0.40)	0.20 (0.11, 0.39)	0.35 (0.19, 0.64)	0.85 [0.67, 1.08]	0.469	0.64 [0.40, 1.04]	**0.065**
RTV C_{max} (µg/mL)	0.40 (0.35, 0.66)	0.62 (0.45, 0.89)	0.92 (0.65, 1.43)	0.92 [0.68, 1.23]	0.547	0.67 [0.54, 0.83]	**0.004**
RTV C_0 (µg/mL)	0.23 (0.11, 0.34)	0.32 (0.16, 0.51)	0.47 (0.08, 0.71)	1.80 [1.02, 3.18]	**0.078**	0.88 [0.56, 1.37]	0.143
RTV C_{12} (µg/mL)	0.16 (0.12, 0.40)	0.20 (0.11, 0.39)	0.34 (0.18, 0.60)	0.85 [0.67, 1.08]	0.469	0.67 [0.41, 1.11]	0.116

*p-value for Wilcoxon rank-sum test; AUC_{0-12} = area under concentration (AUC) vs time curve (0 to 12 hours post-dose); Cl/F = apparent oral clearance; C_{min}= minimum concentration; V/F = apparent volume of distribution; $T_{1/2}$ = elimination half-life; C_{last} = last observed quantifiable concentration; C_0 = initial concentration at time zero; C_{12} = concentration at 12 hours post-dose; C_{min}= minimum concentration, C_{max}= maximum concentration; CI = confidence interval.
#Values are medians (interquartile ranges).

<u>Figure IIe</u>: Median ritonavir concentrations.



Darunavir cord blood median (IQR) was 0.27 (0.14 – 0.55) mcg/mL in 20 samples. Darunavir maternal delivery sample median (IQR) was 2.33 (1.07 – 3.21) mcg/mL in 21 samples. Median (IQR) ratio of cord/maternal darunavir concentrations was 0.15 (0.12 – 0.17) in 16 paired measurable concentrations. Darunavir was below the quantitation limit in 4 of the 20 cord blood samples, but was measurable in all maternal samples. For ritonavir, two cord blood samples were measured using an older assay method with a quantitation limit of 0.094 mcg/mL, and both were below quantitation. Eighteen cord blood samples were measured using a newer assay with a quantitation limit of 0.01 mcg/mL and 7 had measurable ritonavir concentrations, ranging from 0.013 – 0.035 mcg/mL. Combining cord blood results for ritonavir concentration from both assays, 13 of 20 samples were below quantitation. In the maternal delivery samples, 1 was below quantitation, and 20 of 21 had measurable ritonavir concentrations. The median (IQR) was 0.154 (0.106 – 0.279) mcg/mL. In 7 pairs of samples with measurable ritonavir concentrations in both

sample types, the median (IQR) ratio of cord/maternal ritonavir concentrations was 0.07 (0.05 – 0.10).

All the 24 women enrolled in the cohort were on other antiretrovirals in addition to darunavir/ritonavir, as listed in *Table IIa*. Four women (16.7 %) experienced adverse events that were possibly treatment related, including moderately increased alanine aminotransferase (*ALT*), proteinuria, oligohydramnios and intrauterine growth restriction (IUGR). Three infants had birth abnormalities, including a short frenulum and sacral Mongolian spots. None of these birth abnormalities were thought to be related to darunavir or ritonavir exposure. One infant had an adverse event, hyperbilirubinemia, which was thought to be unrelated to darunavir or ritonavir exposure.

DISCUSSION:

Pregnancy is known to modify the activity of some drug metabolizing enzymes, impacting drug exposure.[22] Previous pharmacokinetic data from the IMPAACT P1026s and the Pediatric *AIDS* Clinical Trials Group (PACTG) 353 studies demonstrated decreases in exposure during pregnancy with standard doses of other CYP3A4 metabolized antiretrovirals, including lopinavir, atazanavir, and nelfinavir.[23-27] In subsequent trials, these decreased drug exposures were overcome with increased doses of lopinavir, atazanavir, and nelfinavir during the third trimester of pregnancy, to achieve drug exposures during pregnancy equivalent to those seen in nonpregnant adults.[25,28]

In prior studies of the pharmacokinetics of darunavir during pregnancy, darunavir AUC and C_{max} were substantially decreased in pregnancy with standard darunavir/ritonavir once and twice daily dosing. Darunavir plasma area under the curve (AUC) during the second and third trimester compared with postpartum was reduced by 26% with darunavir/ritonavir 600 mg/100 mg twice daily and by 38-39% with 800 mg/100 mg once a day dosing. Darunavir trough concentrations with twice daily dosing were not different from postpartum but with once daily dosing they were reduced by 63% during the second trimester and 57% during the third trimester compared to postpartum.[4-7] Therefore, the US Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission recommends use of darunavir 600 mg twice daily and not 800 mg once daily during pregnancy because of the reductions in trough darunavir concentrations seen with once-daily dosing during pregnancy. Given the experience with use of increased doses of other protease inhibitors during pregnancy, we hypothesized that increasing the dose of darunavir during pregnancy would increase maternal darunavir drug exposure. However, in the current study, use of an increased dose of 800/100mg DRV/RTV BID during pregnancy resulted in larger differences between darunavir exposure during pregnancy and postpartum, with mean darunavir AUC 38% lower in the second trimester and 36% lower in the third trimester compared to postpartum darunavir AUC with the use of 600/100 mg DRV/RTV BID in the same women.

Darunavir is a substrate and inhibitor of cytochrome P450 (CYP3A) enzymes, and is almost exclusively metabolized by these CYP3A isoforms,[27] while ritonavir, an inhibitor of CYP3A4, is administered as a booster to increase the plasma concentration of darunavir. Darunavir/ritonavir combinations may induce CYP2C9 and CYP2C19 enzymes. Ritonavir inhibition of darunavir metabolism occurs in the liver, and the reduction in plasma ritonavir concentration seen in

pregnancy may lead to reduced ritonavir inhibition of darunavir metabolism and lower darunavir exposure. The increased dose of darunavir we used during pregnancy may have been inadequate to overcome the effect of the reduction in plasma ritonavir exposure. P-gp inhibition by ritonavir may also explain some of the failure of the increased pregnancy dose to result in increased darunavir exposure. Ritonavir can cause mixed inhibition/induction of P-gp, and ritonavir in the gut may lead to reduced darunavir absorption, which could not be overcome by the increased darunavir dose.

Darunavir is known to be highly protein-bound, with about 95% bound to plasma proteins (mainly alpha 1-acid glycoprotein).[27] Plasma *protein binding* of *drugs* to albumin and alpha 1-acid glycoprotein decreases during *pregnancy* due to reduced concentrations of both binding proteins.[27] Previous studies on darunavir protein binding during pregnancy suggest that while there is a marked reduction in total serum concentrations of darunavir in pregnancy, the reduction in protein binding may allow the concentration of unbound darunavir and antiviral activity to be maintained during pregnancy.[4-6]

Examining known PKPD relationships of darunavir (AUC, viral response and protein-adjusted IC_{50}/IC_{90}) in the context of lower exposures and what a clinically relevant decrease in relation to these targets, is critical during pregnancy. Steady state PKPD and efficacy relationships show that trough concentrations (C_{min}) of darunavir are not a good predictor of decrease in viral load, as darunavir exposure-response data were not sufficient to recommend a minimum trough concentration.[17,19] However, the darunavir trough concentrations (C_{min}) during the second and third trimesters, including postpartum (***Table IIb***), were all greater than 10-fold above the mean

darunavir protein-adjusted IC_{50} of 0.055µg/mL (55 ng/mL), 5-fold above the mean darunavir protein-adjusted IC_{50} of 0.55 µg/L for resistant virus,[5] and greater than 10-fold above the mean darunavir protein-adjusted EC_{90} of 0.2 µg/L for wild-type virus. Although lower during pregnancy compared to postpartum, protein bound darunavir concentrations remained well above the viral activity of HIV as shown by its effect on the EC_{50} and EC_{90}, and there were no recorded cases of perinatal transmission of HIV.

Pharmacogenomic drug-drug interactions could also contribute to reduced darunavir concentrations during pregnancy. CYP3A5 polymorphisms have been demonstrated to lower darunavir plasma exposure in participants who express CYP3A5 compared to non-expressors.[29] CYP3A5 activity is extremely dependent on the genetic status of participants due to various genetic polymorphisms related to CYP3A5 activity, leading to either loss or gain of function variants. The most prevalent loss-of-function variant of *CYP3A5* in pregnant and non-pregnant adults is *CYP3A5*3*.[29] This single nucleotide polymorphism (SNP) comprising of a change within intron 3, affects messenger RNA splicing, resulting in a truncated non-functional protein.[29,30] As a result, only participants carrying at least one *CYP3A5*1* (wild-type) allele in pregnancy express functional CYP3A5 activity, while participants who are homozygous for the loss-of-function allele (*CYP3A5*3/*3)* are non expressors of CYP3A5. The impact of pregnancy on these genetic differences in darunavir metabolism are unknown.

Our study has strengths. To our knowledge, this is the first pharmacokinetic study to evaluate the use of an increased darunavir dose (800mg twice daily) during pregnancy. The pregnant patients in this study were followed in a longitudinal pattern throughout pregnancy and postpartum, during which evaluation of clinical findings related to darunavir exposure occurred at regular time

intervals. Because this was a prospective cohort study, confounding, recall and selection biases were minimized. In addition, any random error (misclassifications) in darunavir plasma measurements that arose from the study would tend to be conservative by the prospective nature of this study. The collection of darunavir plasma samples followed a rigorous and stringent protocol, with directly observed dosing aimed at minimizing systematic errors during sample collection. Another strength of this study is that all 24 women (100%) that were studied during the third trimester of pregnancy had complete pharmacokinetic data during the postpartum period.

This study had its limitations. First, this is an observational pharmacokinetic/safety study of a heterogeneous group of pregnant women receiving darunavir for clinical care. There was variation in their background characteristics, and pregnant women who began darunavir/ritonavir but did not tolerate it or demonstrate adequate initial efficacy would be taken off drug and not be eligible for the study. Second, we did not assess the relationship between increased darunavir dosing and genetic resistance to HIV virus in pregnancy. Third, we did not study the precise pharmacokinetic mechanism(s) associated with reduced darunavir concentrations during pregnancy, as this was not part of the study design, although prior pharmacokinetic studies of protease inhibitors in pregnant women show that increased darunavir protein-binding, increased volume of distribution during pregnancy, and increased renal clearance of drugs are likely reasons for lower exposures of darunavir during the 3rd trimester compared to the postpartum period.[31-33]

In conclusion, our findings confirm that darunavir exposure is decreased during pregnancy, and increasing the darunavir/ritonavir dose to 800mg/100 mg twice daily during pregnancy and continuing 600mg/100mg twice daily in the postpartum period failed to significantly increase

darunavir exposure compared to 600 mg twice daily throughout pregnancy and postpartum. This is in contrast to findings with the other protease inhibitors atazanavir, lopinavir and nelfinavir, where increased dosing during pregnancy did improve drug exposure.[23-25] While viral suppression was fairly good in the participants, if achieving darunavir exposure during pregnancy equivalent to that in non-pregnant adults is desired, other strategies, such as increasing the ritonavir dose should be investigated.[32]

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CHAPTER 3

Population Pharmacokinetics of Tenofovir in Pregnant and Postpartum Women using Tenofovir Disoproxil Fumarate.

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ABSTRACT:

Pharmacokinetics of drugs can be affected by physiologic changes during pregnancy. Our aim was to assess the influence of covariates on tenofovir (TFV) pharmacokinetics in pregnant and postpartum women receiving tenofovir disoproxil fumarate (TDF). Population pharmacokinetic parameters estimates and the influence of covariates were assessed using nonlinear mixed effects modeling (NONMEM 7.4). Forty-six women had intensive pharmacokinetic evaluations during the second and third trimesters, and repeated post-partum. A two-compartment pharmacokinetic model with allometric scaling for body weight and first-order absorption best described the tenofovir plasma concentration data. Apparent oral clearance (CL/F) and volume of distribution (Vss/F) were increased during pregnancy. Weight, serum creatinine (SCr), pregnancy, albumin and age were associated with TFV CL/F during univariate assessment, but in the multivariate analysis, changes in CL/F and Vss/F were only associated with enhanced renal function. Due to greater weight and lower SCr during pregnancy, CL/F was 28% higher during pregnancy compared to postpartum. In the final model, CL/F (L/h) was described as $2.07*(SCr/0.6)^{0.65}*Weight^{0.75}$, with a low between subject variability (BSV) of 24%. The probability of target attainment (proportion of TFV simulations exceeding AUC>1.99 mcg*h/mL, the 10^{th} percentile of average TFV exposure for non-pregnant historical controls) was 68%, 80%, 87%, and 93% above target with 300mg, 350mg, 400mg and 450mg of TDF respectively during pregnancy, and 88%, 92%, 96% and 98% above target with same doses in postpartum women. Dose adjustment of TDF during pregnancy is not generally warranted but any modification should be based on weight and renal function.

INTRODUCTION:

Tenofovir Disoproxil Fumarate (TDF), a diester prodrug of tenofovir (TFV), is a backbone component of combination antiretroviral (ARV) therapy currently recommended by the US perinatal guidelines for the management of pregnant women living with HIV for preventing perinatal infection.[1] Following oral administration and absorption, TFV is transported inside cells and phosphorylated by intracellular kinases to tenofovir-monophosphate (TFV-MP), and then its active metabolite, tenofovir-diphosphate TFV-DP.[2] Tenofovir is predominantly eliminated unchanged in the urine by a combination of active tubular secretion and glomerular filtration.[3] Due to several physiological changes that occur during pregnancy (primarily increased renal clearance), plasma concentrations of TFV are decreased during the 2nd and 3rd trimesters of pregnancy, returning to baseline in the postpartum period.[4] In addition, relative decreases in plasma TFV exposure significantly vary by age, weight, and other physiologic parameters.[5,6] An understanding of TFV between-subject and within-subject variability patterns in pregnant and postpartum women is vital to determining the key factors influencing changes in TFV exposure.

A population pharmacokinetic (POPPK) approach allows for the development of a model that describes the time course of drug concentrations, and integrates between-subject and within-subject variability. A POPPK analysis of TFV by Hirt and colleagues assessed TFV plasma concentrations in 38 women living with HIV who received 600mg of TDF at delivery and 300 mg daily for 7 days postpartum, and demonstrated an acceptable materno-fetal transport of TFV of approximately 60%.[7] In another POPPK study of 186 women with HIV (including 46 pregnant women on 300 mg once daily TDF), Benaboud *et al* reported that pregnant women had a 39% higher apparent TFV clearance during delivery compared to non-pregnant women. The Benaboud

POPPK model was unable to evaluate gestational-dependent changes on TFV clearance, or measures of kidney function (serum creatinine concentrations or estimated glomerular filtration rate), limiting the ability to inform dosing recommendation.[8] While these pregnancy POPPK studies of TFV provided critical insights into sources of intra and inter-individual variability in TFV disposition during pregnancy, both studies were conducted using sparse PK data. Intensive PK data may provide an improved understanding of intra and inter-individual variability in TFV disposition during pregnancy and postpartum.

Our objective was to evaluate the impact of clinical factors in pregnant and postpartum women living with HIV that affect TFV PK (when administered as 300mg of TDF daily) within a large, well characterized and diverse population of women.

METHODS:

Data were collected as part of International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) protocol P1026s, a multi-center, non-blinded, prospective Phase IV study of the pharmacokinetics and safety of selected antiretrovirals (ARVs) in HIV infected pregnant women. This analysis included pregnant women receiving 300mg of tenofovir disoproxil fumarate (TDF). The study protocol, the informed consent documents, and all subsequent modifications were reviewed and approved by the local institutional review board (IRB)/Ethics Committee responsible for oversight of the study. The study followed all relevant human subject research guidelines. All participants provided signed informed consent before participation.

Pregnant women living with HIV were eligible for enrollment in the second and third trimesters if they were receiving TDF 300mg once daily as part of clinical care. All ARVs were prescribed by

the participants' clinical care providers and dispensed by local pharmacies, as per local standard of care. Maternal exclusion criteria were current use of medications known to interfere with tenofovir metabolism (including acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides and non-steroidal anti-inflammatory drugs), presence of severe renal disease, liver disease, and other clinical or laboratory toxicity that, per site investigators, would require a change in the antiretroviral regimen.

Clinical and laboratory data

Maternal demographic and clinical information were abstracted from the medical record, including maternal age, gestational age, serum creatinine, serum albumin, maternal race and ethnicity, weight and concomitant medications. Plasma HIV-1 RNA assays were performed locally. Study mothers and infants were followed through six months after delivery. Gestational age at the time of delivery, birth weight and HIV infection status data were collected from the infant's medical record. Physical examinations were performed on neonates after delivery, and infant laboratory evaluations were performed as clinically indicated. Maternal clinical and laboratory toxicities were assessed through clinical and laboratory evaluations on each pharmacokinetic sampling day, at delivery, and at 24 weeks postpartum. Any additional toxicities noted as part of clinical care were also recorded. The study team reviewed toxicity reports on monthly conference calls, although each participant's physician was responsible for toxicity management. The Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (August 1992), was used to grade adverse events for study participants. All toxicities were followed through resolution or 24 weeks postpartum.

Sample collection and pharmacokinetic sampling schedule

Intensive PK samples were collected at 20-26 weeks gestation for 2nd trimester PK evaluation; at 30-36 weeks gestation for 3rd trimester PK evaluation and between two and 12 weeks after delivery for postpartum evaluation. Plasma samples were drawn immediately prior to an observed dose and at 1, 2, 4, 6, 8, 12, and 24 hours post-dose. Paired maternal and cord blood samples were collected at delivery. All plasma samples were collected at steady state. The steady-state PK profiles collected included 688 plasma tenofovir concentrations from 46 women during the second trimester (n=7), third trimester (n=41) and postpartum (n=38).

Bioanalytical methods

Plasma samples collected for PK assays were stored at ≤-70°C until analysis. Tenofovir concentrations were measured by a previously described validated, liquid chromatography−mass spectrometry (LC-MS/MS) method.[4] The linear range was 10 to 1,500 ng/mL, with a lower limit of detection for TFV of 10 ng/mL. Accuracy and precision were within ± 20% at 10 ng/mL and ± 15% at other quality control concentrations.

Covariate data

The potential impact of clinical covariates, such as maternal age, trimester of pregnancy, maternal weight gain, gestational age, serum creatinine, serum albumin, maternal race and ethnicity were evaluated for inclusion in the model. Baseline covariate parameters were obtained from the medical records, and defined using the last recorded values before the first dose of TDF in pregnant women. There were very few missing covariate laboratory values (2%), they were treated as

follows: the median value across all subjects was used. For missing pre-pregnancy weight, the post-partum weight was used.

Population PK base structural model development

Population pharmacokinetic analyses were constructed in the nonlinear mixed effects modelling (NONMEM®) software (Version 7.4, ICON Development Solutions, Ellicott City, Maryland). R software (version 3.0.1) was used for dataset construction, graphical inspection, statistical analysis, model diagnostics and final model development, and Wings for NONMEM 7.4 was used for bootstrap analysis. The first order conditional estimation method with interaction (FOCE-I) was used for model fitting.

Multiple absorption mechanisms including first-order, zero-order and sequential zero- and first order absorption with and without an absorption lag time were modeled using a two-compartmental approach that assumed plasma as the central compartment, from where blood samples for TFV concentration measurements are obtained and TFV is eliminated, and a peripheral compartment representative of less well perfused tissues such as muscle and fat. An exponential model was used to describe inter-individual (between-subject) variability. All PK parameters were assumed to be log-normally distributed around the population mean value, θ (equation A):

$$\theta_i = P_a * exp^{\eta_a} \qquad (A)$$

where P_a is the estimate of the PK parameter (e.g. TFV clearance) in individual a, θ is the population typical mean of the PK parameter, and η_a is the between subject (inter-individual) variability, describing the deviation from the typical population parameter for the a^{th} participant on TDF. Thus, as described in equation A, the θ_i value is a function of the typical population value

for the PK parameter and the random effect of the individual variance from the typical population mean. Inter-occasion variability (IOV) was also assessed for inclusion in the model.

Power, proportional, additive, and combined (additive and proportional) residual error models were also evaluated. Competing PK models were selected based on minimization of objective function value, precision of parameter estimates, visual inspection of goodness-of-fit plots and physiologically reasonable and/or statistically significant parameter estimates. Model discrimination was based on relative objective function values (OFVs) computed in NONMEM as −2× log likelihood, and the number of estimable parameters (p) in the model: Akaike Information Criterion (AIC) = OFV + 2p. The AIC is a test used to evaluate how well a model fits the data it describes. The AIC penalizes models that use more independent parameters to prevent over-fitting.

Covariate model development:

The covariate model was developed after the basic model was constructed. Body weight (WT) was incorporated into the model with allometric scaling before assessment of other covariates. Standard allometric exponents were utilized, $WT^{0.75}$ for apparent clearance (CL/F) and apparent inter-compartmental clearance (Q/F); and isometric exponent ($WT^{1.0}$) for central compartment (V_1/F) and the peripheral compartment (V_2/F). The sum of V_1/F and V_2/F in this two compartment model equals the apparent volume of distribution at steady state (Vss/F). The impact of weight was evaluated as pre-pregnancy weight, current weight, and a hybrid approach with different influences of pre-pregnancy weight and weight gain. The hybrid approach included additional scalars added to the weight gain for CL/F and Vss/F such that the weight gain of pregnancy would not have the same impact as the pre-pregnancy weight. While the hybrid approach worked best in

the initial analysis, the bootstrap of the final hybrid model showed unacceptable 95% CI and was abandoned in favor of total weight, which performed better than pre-pregnancy weight. Covariate analysis was performed on CL/*F and Vss/F*, in a stepwise manner, using the changes in the objective function value – a reduction of ≥ 3.84 (~ P < ~0.05) significance threshold for forward step, followed by a reduction of ≥ 10 (P < ~0.001) significance threshold for backward elimination. Biologically plausible covariates were evaluated, including maternal age, trimester of pregnancy, serum creatinine, albumin, gestational age, and concomitant ritonavir use. All potential covariates identified in the forward screen were combined into a single model to start the backward analysis. Using the resulting new model, individual covariates were removed one by one. If the objective function increased with removal of covariate by less than 10, it was eliminated from the model. The process was repeated until no additional factor could be removed without significant worsening of the model.

Continuous covariates (e.g. gestational age and serum creatinine) were modeled using a median-normalized power model (equation C), where P_a represents the population prediction of the parameter, COV_i represents the value of the i^{th} continuous covariate, COV_{median} represents the median value of the covariate in the population, θ_1 represents the population typical value of the parameter, and θ_2 represents an estimated parameter describing the fixed effect of the covariate on the PK parameter.

$$P_a = \theta_1 * (\frac{COVi}{COVmedian})^{\theta 2} \qquad (C)$$

Categorical covariates (e.g. ritonavir use – yes or no) were described using a power model – Equation D, where variables are indicated as binary (0 or 1). θ_1 represents the parameter estimate

for an individual with COV coded as 0, and θ_2 represents the change in PK parameter relative to when COV is equal to 1.

$$P_a = \theta_1 * \theta_2{}^{COVi} \quad (D)$$

After identifying significant covariates, additional assessment of the random error structure was investigated.

The ability of body size models to reduce the unexplained between-subject variability and improve the goodness of fit of the model was also explored. To investigate the effect of weight, based on visual inspection, goodness of fit plots, likelihood ratio testing (by a decrease in OFV), and model stability assessment, the covariate relationship between CL/F and V_{ss}/F that includes an adjustment for the weight of each subject individually using normalization to weight and allometric scaling with an exponent (θ_2) were defined as follows in Equations E and F:

$$\frac{CL}{Fi} = \left[\theta_1 * \left(\frac{WT}{WT_{median}}\right)^{\theta 2}\right] * exp^{(\eta 1i)} \quad (E)$$

$$\frac{Vss}{Fi} = \left[\theta_3 * \left(\frac{WT}{WT_{median}}\right)^{\theta 4}\right] * exp^{(\eta 1i)} \quad (F)$$

Where CL/F_i represents the body-weight normalized apparent clearance of the *i-th* individual, Vss/F_i represents the body-weight normalized apparent volume of distribution of the *i-th* individual, θ_1 represents the typical values for apparent clearance, θ_2 represents the allometric power exponent for clearance, θ_3 represents the typical values for apparent volume of distribution, θ_4 represents the allometric power exponent for apparent volume of distribution, η_i *re*presents the between-subject variability random effect with a mean of 0 and variance of w^2, *WT* represents the body weight of the *i-th* individual, and WT_{median} represents the median weight. Weight was measured in kilograms. The body size model best described and fitted the PK data.

Model checking and evaluation, diagnosing errors, validation and reliability testing

Goodness-of-fit (GOF) plots generated for model evaluation and verification included observed versus predicted data plots, and weighted residuals versus population predicted values for final model evaluation. Bootstrapping of the final model was performed by creating 1000 simulated datasets by resampling with replacement from the original dataset. Model parameters based on the original dataset were compared against the bootstrap results. Visual predictive check (VPCs) plots were generated on the basis of the 1,000 simulations. The VPC plots showed the 10th, 50th and 90th percentiles of observed data over time calculated from 1000 Monte Carlo samples (simulated using the model, the parameter estimates and the design of the data set).

Simulation of dosage regimens:

A Monte Carlo simulation was performed using the final PK model with covariates to predict the distribution of plasma TFV concentrations. Four dosage regimens were studied, as follows: 300mg, 350mg, 400mg and 450 mg of TDF, with administration every 24 hours. We simulated the profiles of 1000 pregnant and 1000 postpartum women with a set of covariates resampled among the observed covariates of included patients, and a vector of random effects drawn from the estimated distribution. The concentration–time profiles at steady state for the four TDF dosage regimens were simulated throughout pregnancy, and continued till 12 weeks postpartum based on the distribution of clinical characteristics from our study. The proportion of TFV simulations in pregnant and postpartum women exceeding AUC >1.99 mcg*h/mL, and the summary statistics (median, 2.5^{th} and 97.5^{th} percentiles) were obtained.

RESULTS:

Study Population:

The demographic characteristics are summarized in ***Table IIIa***. A total of 46 subjects provided 688 plasma samples (8 plasma PK sample collections from 7 pregnant women in the second trimester, 8 plasma PK samples from 41 pregnant women in the third trimester, and 8 plasma samples from 38 women postpartum) were included in the POPPK analysis. Briefly, median maternal age, pre-pregnancy weight, and weight gain were 31 years (interquartile range 26.8-34.2), 76.4 kg (range 66.3-96.9) and 6.85 kg (range 4.15–11.40), respectively. 39% of participants in the analyzed dataset were Hispanic, 35% were Black, 20% White non-Hispanic, 2% Asian/Pacific Islander, 2% more than one race, and 2% unknown. Thirty-nine (84.8) of the women were on concomitant ritonavir boosted protease inhibitor ARVs as follows: 24 women (52.2%) were on atazanavir/ritonavir, 12 women (26.1%) were on lopinavir/ritonavir, 2 women (4.3%) were on saquinavir/ritonavir, and 1 woman (2.2%) was on fosamprenavir/ritonavir.

Maternal-fetal cord blood sampling:

Paired maternal and cord blood samples were collected once - at the time of delivery. The median (IQR) concentration of TFV in maternal plasma samples collected at delivery was 62.4 (44.1, 73.4) ng/mL, and in umbilical cord blood samples was 56.7 (37.0, 76.5) ng/mL. Cord blood to maternal plasma concentration ratio was 0.91 (0.76, 1.03) for all mother/infant pairs.

Table IIIa: ***Baseline characteristics of participants taking Tenofovir Disoproxil Fumarate (TDF) (n=46)***

Characteristics	Median (percentage or IQR)
Participant's age at 1st visit (yrs)	30.94 (IQR 26.80, 34.23)
Number of women from each visit	
Second trimester	7 (8.1%)
Third trimester	41 (47.7%)
2-3 weeks postpartum	3 (3.5%)
6-12 weeks postpartum	35 (40.7%)
Race	
Hispanic	18 (39.1%)
Black	16 (34.8%)
White, non-Hispanic	9 (19.6%)
Asian/Pacific Islander	1 (2.2%)
More than 1 race	1 (2.2%)
unknown	1 (2.2%)
Pre-pregnancy weight (kg)	76.40 (IQR 66.30, 96.88)
Weight (kg) in the 3rd trimester (kg)	80.6 (IQR 50.8, 121.9)
Weight gain in 3rd trimester (kg)	6.85 (IQR 4.15, 11.40)
Concomitant medications	
Ritonavir boosted PI	39 (84.8%)
- Atazanavir/ritonavir	24 (52.2%)
- Lopinavir/ritonavir	12 (26.1%)
- Fosamprenavir/ritonavir	1 ((2.2%)
- Saquinavir/ritonavir	2 (4.3%)
Emtricitabine	33 (71.7%)
Lamivudine	10 (21.7%)
Zidovudine	7 (15.2%)
Efavirenz	3 (8.7%)
Nevirapine	4 (6.5%)

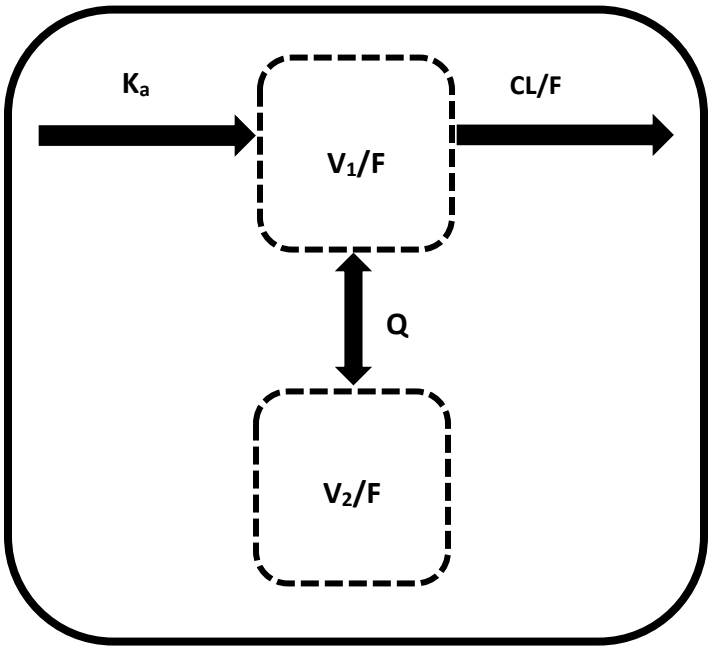
IQR – Interquartile range

POPPK Structural Base Model:

A two-compartment model (a central and a peripheral maternal compartment) with first order absorption, with elimination assumed to be from the central compartment (***Figure IIIa***) best described our data. This two-compartment model structure (a central and a peripheral compartment) was used as the base model. Due to lack of adequate sampling time points during the absorption phase (Day 0 and 1), complex absorption models could not be characterized, and a

simpler first-order absorption model (K_a fixed to 6.93 hr^{-1}) was chosen. A value of K_a = 6.93 hr^{1} was estimated based on the base model, but subsequently fixed due to low precision of the estimate.

Figure IIIa: Model structure of tenofovir population pharmacokinetics



CL/F, V_1/F, V_2/F, Ka, and Q represent apparent clearance, volume of central compartment, volume of peripheral compartment, absorption rate constant, and inter-compartmental clearance respectively.

The robustness of the fixed value was further verified using a sensitivity analysis by varying K_a from 0.1 to 10 hr^{-1}; change in the OFV and the variance model parameter values indicated the chosen value of 6.93 hr^{-1} to be appropriate. Between-individual variability was described by an exponential model, and with a residual power error model, provided the best description of the data (based on a goodness of fit plots and lower objective function (OFV >-51). Addition of inter-occasion variability (IOV) on CL/F and V_{ss}/F further led to a reduction in objective function values (P<0.001) and improved model fit.

Population pharmacokinetic analysis:

A total of 688 plasma samples (8 plasma PK sample collections from 7 pregnant women in the second trimester, 8 plasma PK samples from 41 pregnant women in the third trimester, and 8 plasma samples from 38 women postpartum) were available for POPPK modeling. Most TFV peak plasma concentrations during pregnancy and postpartum were observed at 0.5-2 hours (***Figure IIIb*** and ***Figure IIIc***), consistent with what is known about the time to maximum plasma concentration (T_{max}) of TFV in participants taking TDF. No participant had TFV concentrations below the lower limit of detection for TFV of 10 ng/mL. During pregnancy, one patient received her post-dose TDF late (***Figure IIIb***).

Figure IIIb: Spaghetti plots of tenofovir concentrations versus time (3rd Trimester)

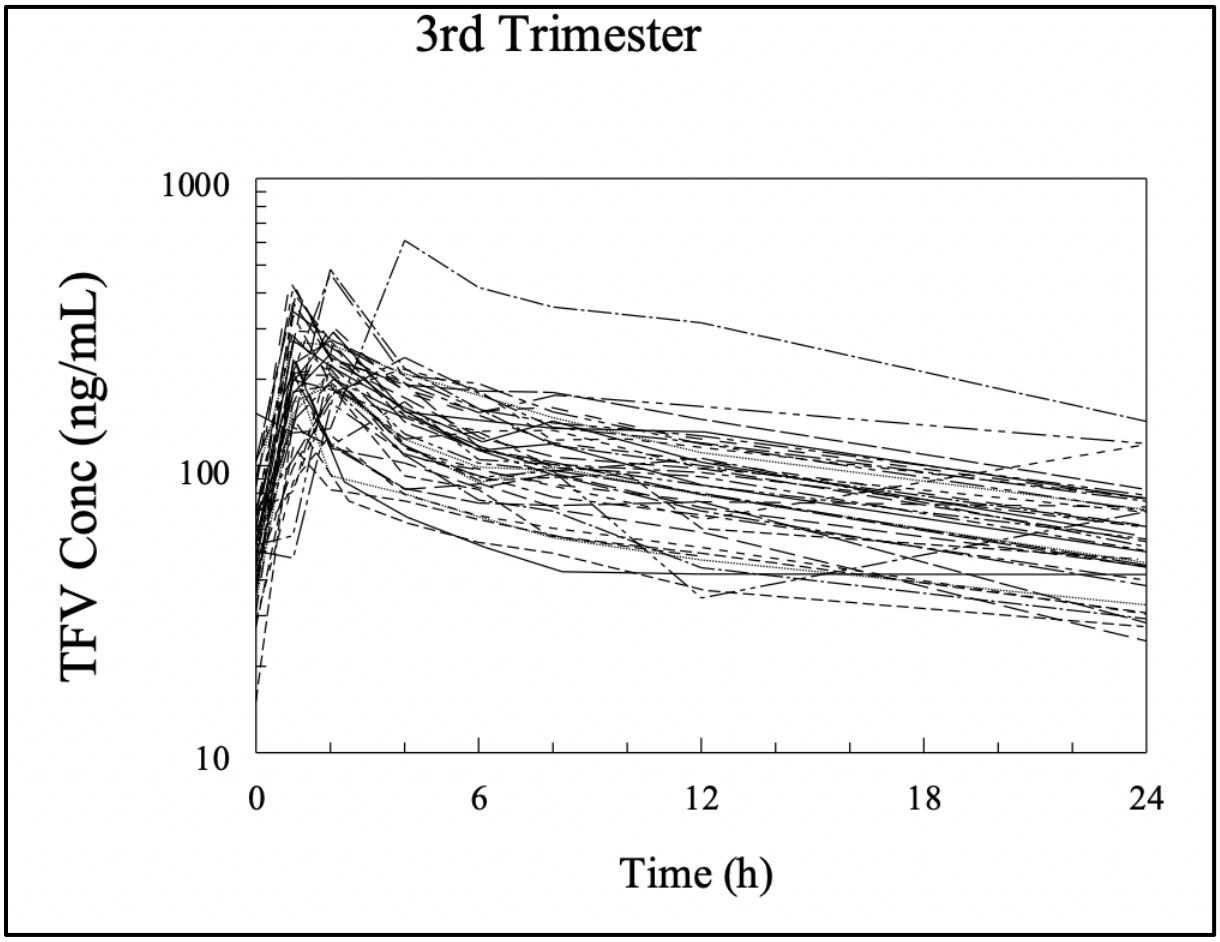


Figure IIIc: Spaghetti plots of tenofovir concentrations versus time (postpartum).

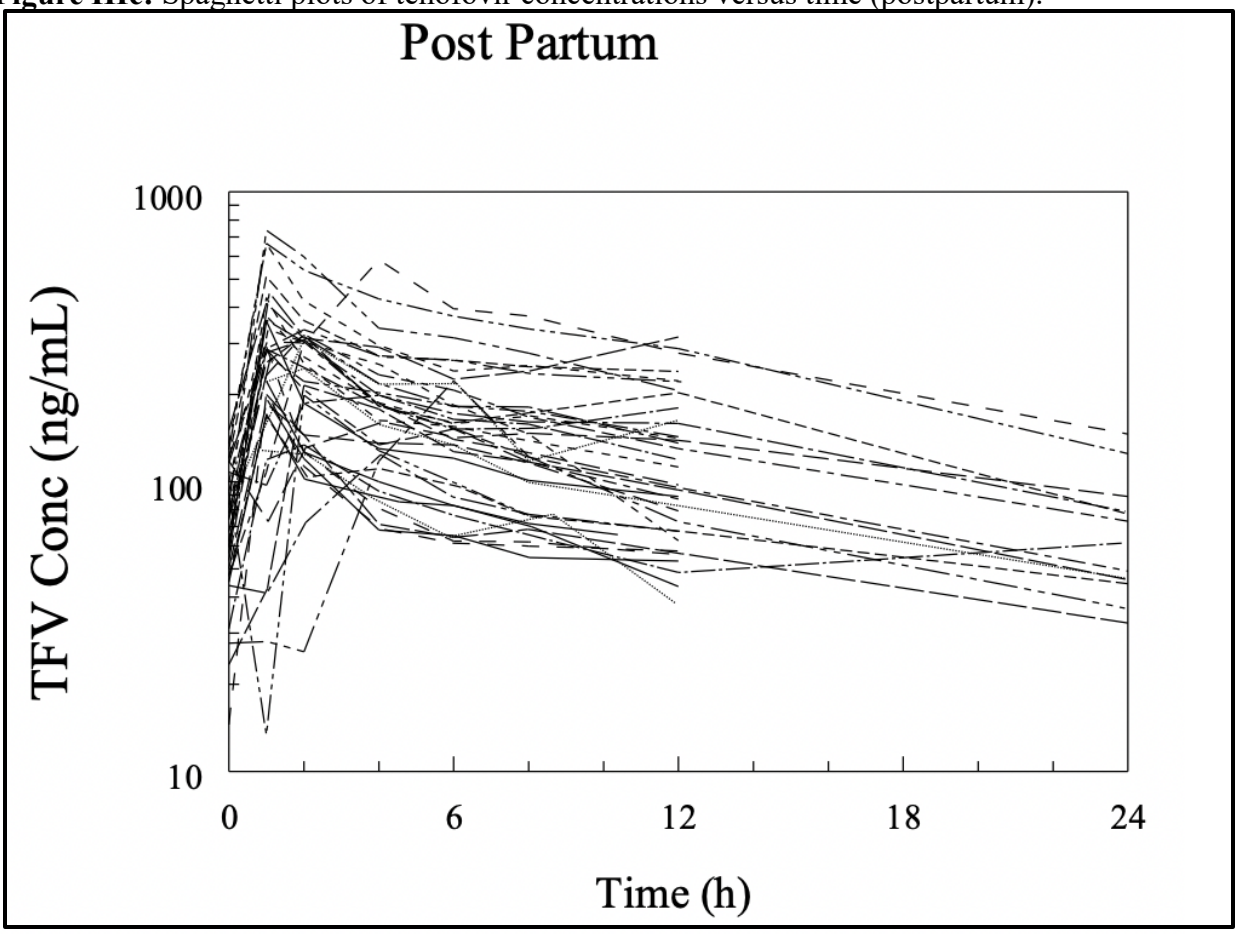


Table IIIb shows the change in objective function values following inclusion of covariates into the base population PK model. CL/F and Vss/F were increased during pregnancy. For univariate inclusion of covariates for CL/F, serum creatinine (ΔOFV = -16.174), pregnancy status (ΔOFV = -5.376), serum albumin concentration (ΔOFV = -5.051), gestational age (ΔOFV = -3.986), and maternal age (ΔOFV = -6.119) had a significant relationship with TFV CL/F. Insignificant covariates included the use of concomitant ritonavir (ΔOFV = -2.007). The univariate inclusion of covariates on V_{ss}/F led to decrease in the OFV for pregnancy status (ΔOFV = -6.474), gestational age (ΔOFV = -5.726), maternal age (ΔOFV = -5.849), serum creatinine (ΔOFV = -14.627), and

serum albumin (ΔOFV = -7.401) – ***Table IIIb***. The only significant covariates for CL/F obtained in the multivariate analyses was creatinine clearance (ΔOFV = −16.699; $P < 0.001$). There were no significant covariates for V_{ss}/F in the multivariate analysis.

Table IIIb: Change in objective function value by univariate and multivariate inclusion of covariates into base population pharmacokinetic model.

Covariate	**Univariate analysis**		**Multivariate analysis**	
	Δ Objective function	**Univariate Estimate**	**Δ Objective function**	**Retained in model**
Covariates for apparent clearance (CL/F)				
1. Pregnancy status: Cov^{PREG}	-5.376	1.18	0.707	No
2. Gestational age: $(GA/20)^{Cov}$	-3.986	0.25	-2.114	No
3. Age: $(Age/31)^{Cov}$	-6.119	-0.33	-1.977	No
4. Serum creatinine: $(SCR/0.6)^{Cov}$	-16.174	-0.7	-16.699	Yes
5. Serum albumin: $(ALB/3.6)^{Cov}$	-5.051	-0.43	-2.343	No
6. Ritonavir: COV^{RTV}	-2.007	0.932	ND	NA
Covariates for V_{ss}/F				
1. Pregnancy status: Cov^{PREG}	-6.474	1.3	-0.019	No
2. Gestational age: $(GA/20)^{Cov}$	-5.726	0.48	-2.593	No
3. Age: $(Age/31)^{Cov}$	-5.849	-0.42	-2.245	No
4. Serum creatinine: $(SCR/0.6)^{Cov}$	-14.627	1.04	-1.913	No
5. Serum albumin: $(ALB/3.6)^{Cov}$	-7.401	-0.89	-2.195	No
6. Ritonavir: COV^{RTV}	-1.647	1.02	ND	NA

The scatterplot of TFV clearance versus serum creatinine (a marker for renal function) (***Figure IIId)***, demonstrated an inverse relationship (more marked in pregnancy compared to postpartum). ***Figure IIIe*** shows box-plots for TFV CL/F by pregnancy status - pregnant versus postpartum. The clearance of TFV was 28% higher in pregnant women compared to postpartum women.

Figure IIId: *Apparent TFV clearance versus serum creatinine clearance (marker of renal function). Solid lines represent lines of identity for pregnant women; while interrupted lines represent lines of identity for non-pregnant (postpartum) women. Serum creatinine was measured in mg/dL.*

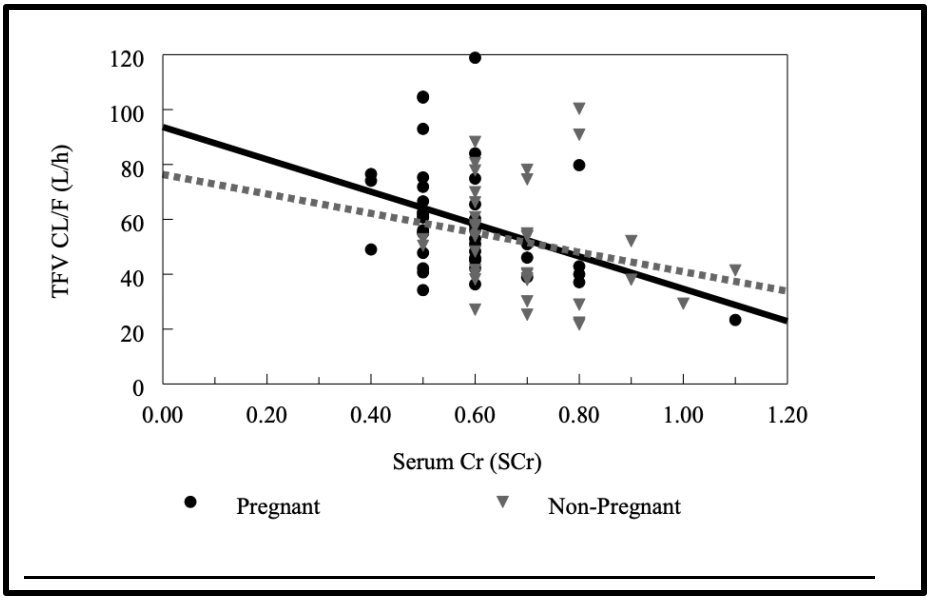
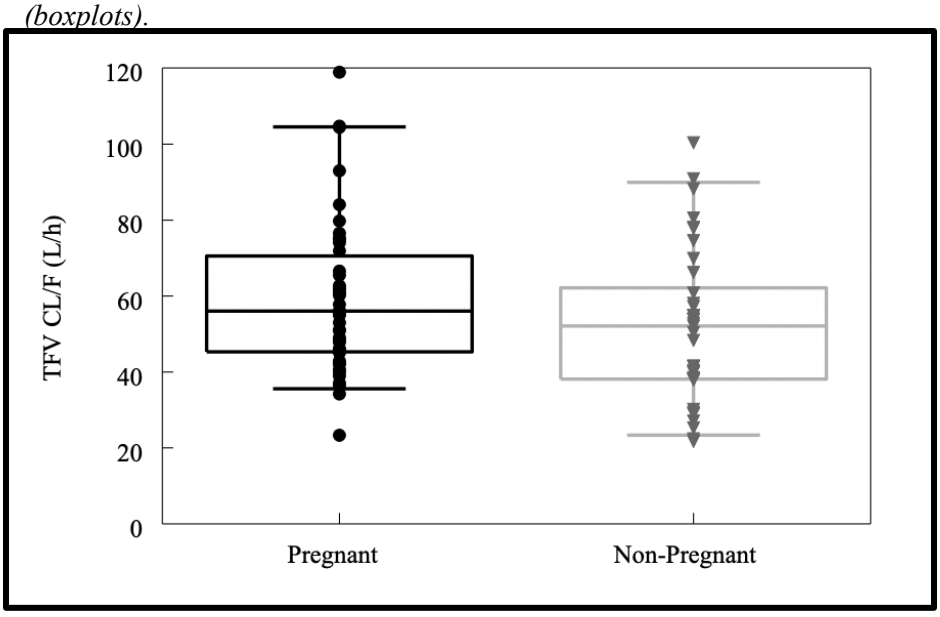


Figure IIIe: *Boxplot of empirical Bayesian estimates of apparent TFV clearance in pregnant and non-pregnant (postpartum) women. Horizontal line, median; box, quartiles; and whisker, range of the data (boxplots).*



Model Evaluation and Validation

Model performance was evaluated using various plots, including scatter goodness-of-fit plots of the individual predicted versus observed plasma TFV concentrations, conditional weighted residuals versus concentration/time, and plot of distribution of CL/F and V_{ss}/F. The model-predicted and individual-predicted concentrations versus observed TFV concentrations using the final model are represented as scatterplots in ***Figure IIIf*** and ***Figure IIIg,*** respectively. Model predictions were symmetrically distributed around the line of identity indicating that the model adequately described TFV disposition. The model-predicted and individual predicted values agreed with the observed values across the range of predicted concentration/time and the distributions of CL/F and V_{ss}/F, and followed a log-normal distribution. The plots of the conditional weighed residuals (CWRES) fitted the data well (***Figure IIIh***).

Model stability, reliability and validity, assessed by bootstrapping the final model, including a total of 1000 bootstrap replicates, minimized successfully with 998 successfully runs. The estimated PK parameter values based on the original dataset were in good agreement with the medians of the parameter values estimated from the bootstrap replicates. Internal quantification by simulation using visual predictive checks (VPC) showed close agreement. The visual predictive check (VPC) plots during pregnancy (***Figure IIIi***) and postpartum (***FigureIIIj***) as a function of time, indicate a good predictive performance of the model.

Figure IIIf: Goodness of fit plot – model predicted (population)

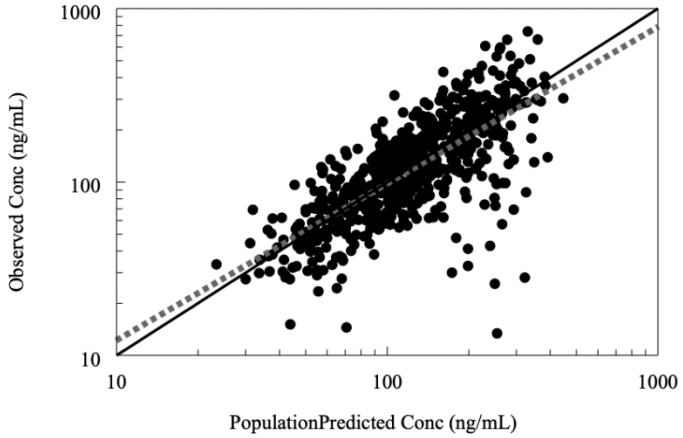


Figure IIIg: Goodness of fit plot – individual predicted

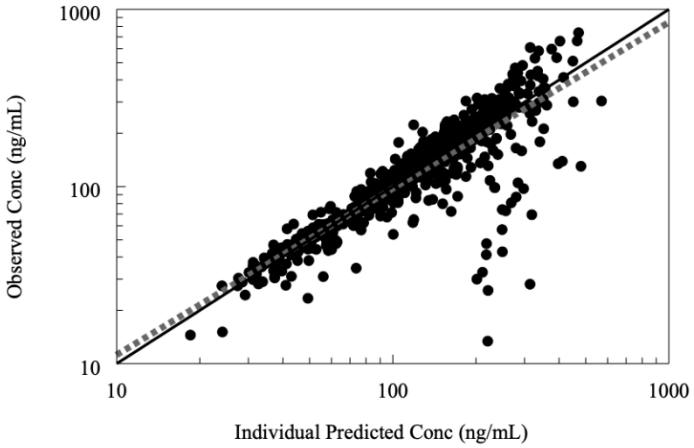
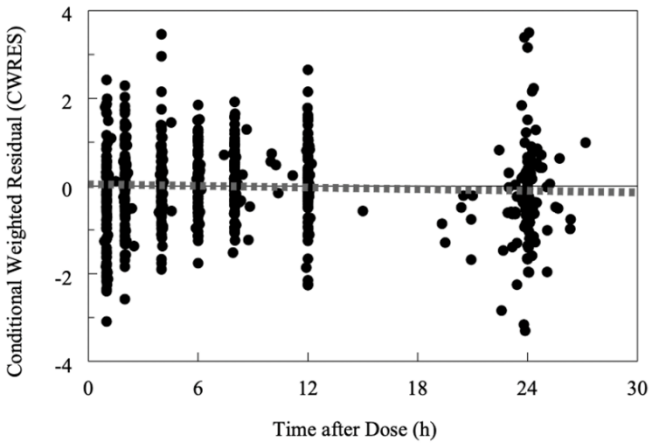


Figure IIIh: Conditional weighed residual for final model



<u>Figures IIIf-h:</u> *Goodness-of-fit diagnostic plots of observed TFV concentrations versus predicted values in the population (**IIIf**), individual predicted TFV concentrations (**IIIg**), and conditional weighted residual for the final model (**IIIh**). Solid lines represent lines of identity for pregnant women; while interrupted lines represent lines of identity for non-pregnant women. A symmetrical distribution around the line of identity is observed indicating the goodness of fit of the model.*

Figure IIIi: VPC plot for Pregnancy – 5th, 50th and 95th percentile.

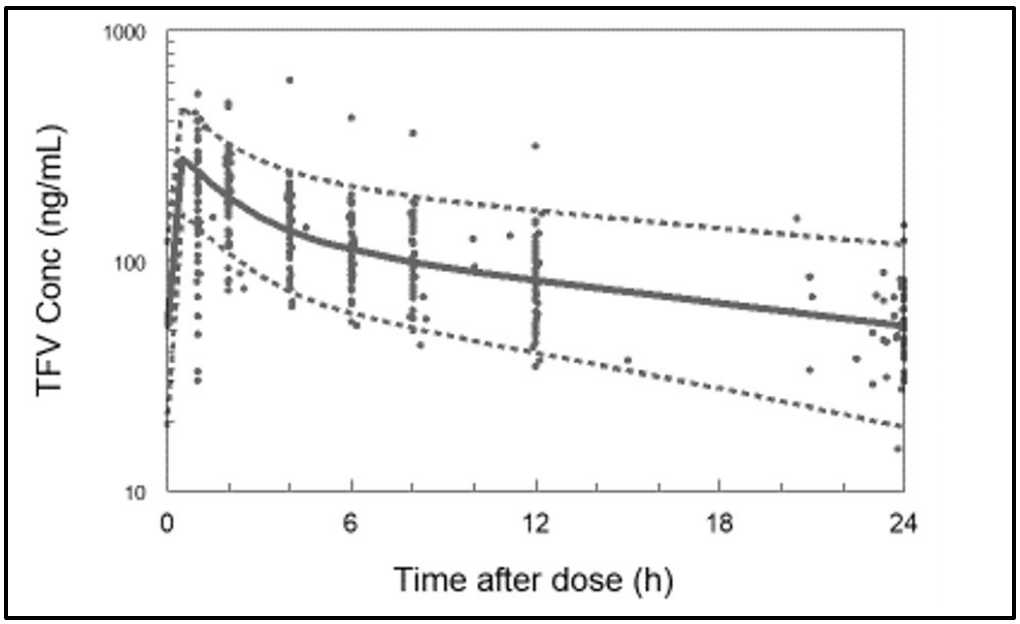
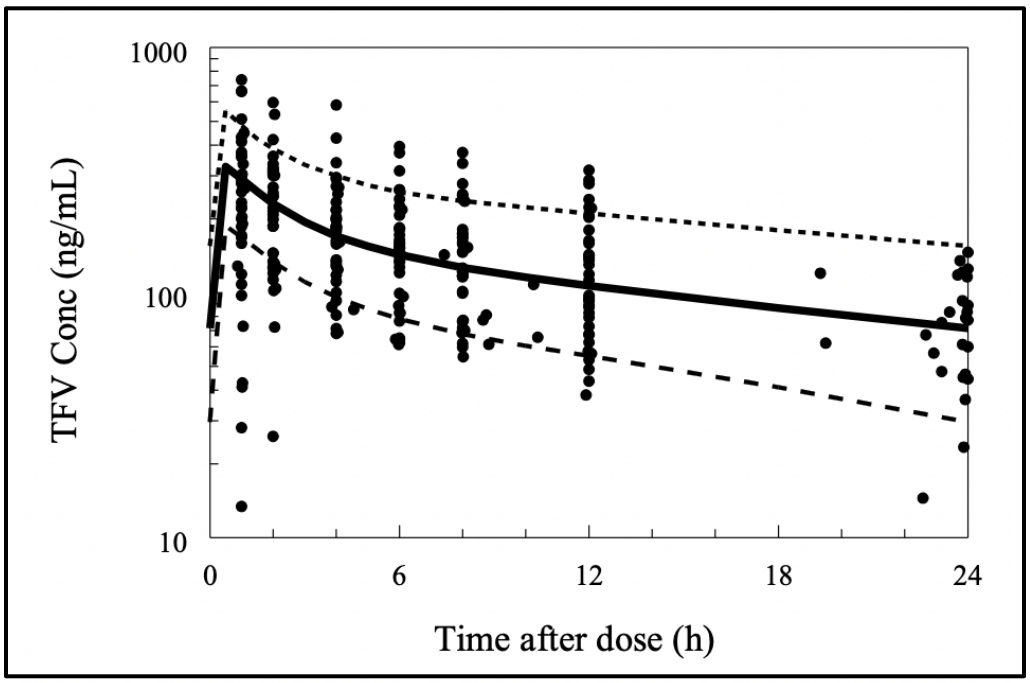


Figure IIIj: VPC plot for Postpartum – 5th, 50th and 95th percentile.



POPPK Final Model:

Typical values for clearance, inter-compartmental clearance, central and peripheral volumes of distribution are as shown in ***Table IIIc***. In the final model, the equation to estimate the apparent clearance of TFV was:

CL/F (L/h) = 2.07*(Serum creatinine/0.6)$^{0.65}$*Weight$^{0.75}$

Where serum creatinine was measured in mg/dL, and weight in kilograms. The variability in the estimate of CL/F, expressed as percent coefficient of variation (%CV) was 24%, while the variability in the estimate for Vss/F was 25%. Inter-occasion variability was modeled to CL/F (IOV-CL/F), and had a variability estimate of 26%.

Table IIIc: Final model: Parameter estimates and variability for Tenofovir Pharmacokinetics.

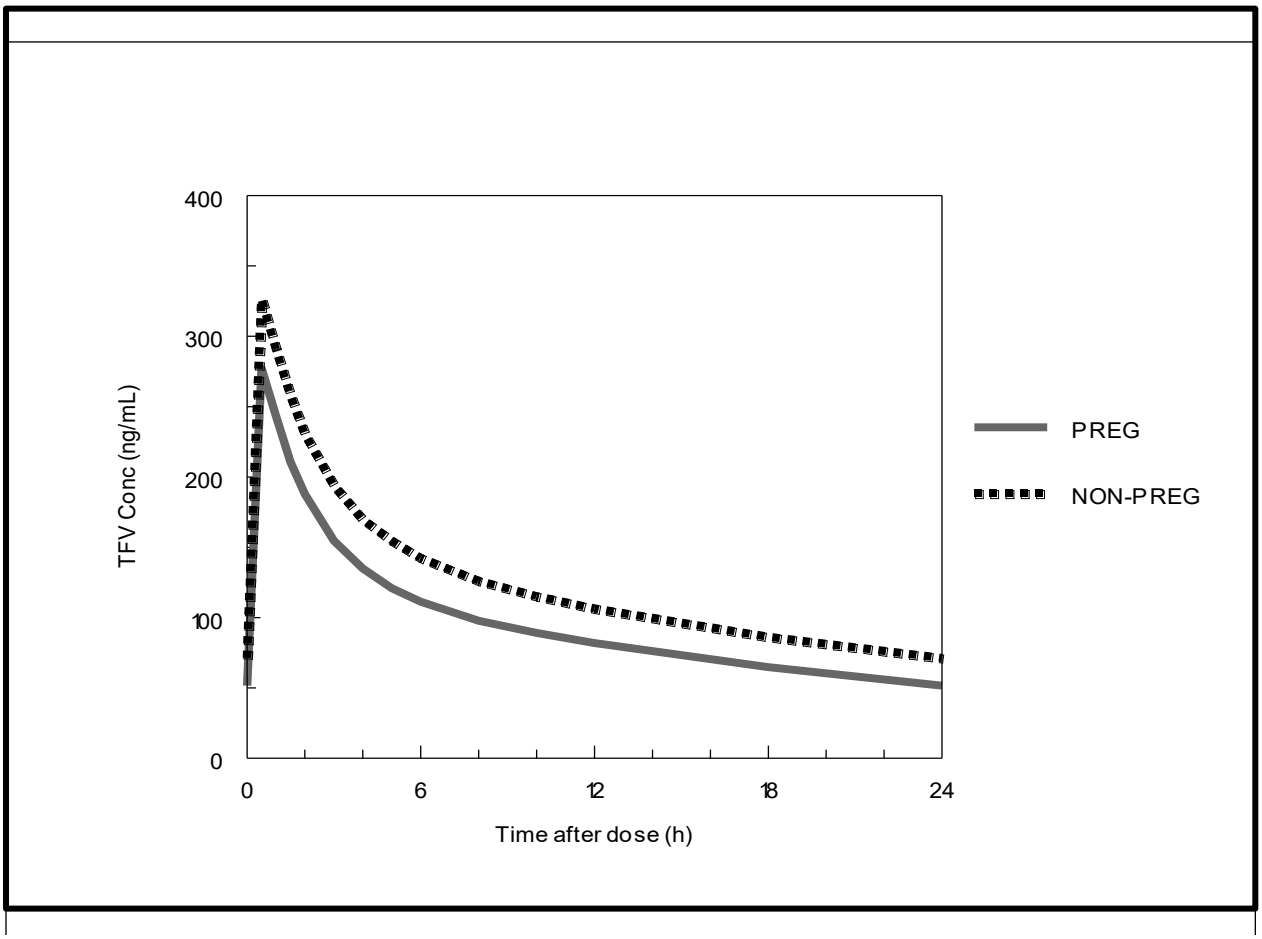
Parameter	**Final model**		**Bootstrap analysis final model**		
Structural (base) Model	**Population Median**	**%RSE**	**Median**	**2.5% percentile**	**97.5% percentile**
Cl/F (L/hr/kg$^{0.75}$)	2.07	0.09	2.00	1.85	2.16
V_1/F (L/kg)	6.37	1.07	6.34	4.87	8.70
V_2/F (L/kg)	9.55	1.20	9.60	8.12	12.30
K_a (hr^{-1})	6.93	NA	NA	NA	NA
Q (L/hr/kg$^{0.75}$)	3.14	0.95	3.15	0.05	4.69
SCR Factor	-0.65	0.13	-0.66	-0.90	-0.36
Statistical Model					
Between subject variability (BSV)					
Vss/F	25%	21%	24%	5%	40%
CL/F	24%	12%	23%	17%	29%
IOV- CL/F	26%	15%	-	-	-
Residual variability					
Proportional (% CV)	3.0%	2.6%	3.0%	1.1%	6.0%
Power Exponent	1.43	0.08	1.38	1.25	1.54

V_{ss}/F , volume of distribution at steady state; IOV, Inter-occasion (within subject) variability; CL/F, apparent clearance; k_a, absorption rate constant; V_1/F, apparent volume of distribution of the central compartment; V_2/F, apparent volume of distribution of the peripheral compartment; Q, inter-compartmental clearance; SCR, Serum creatinine; NA, Not applicable; %RSE, relative standard error of parameter estimate. Between subject variability and residual (proportion) variability estimates are shown as percent coefficient of variation (% CV).

Simulation of TDF dosage regimens and Probability of Target Attainment (PTA):

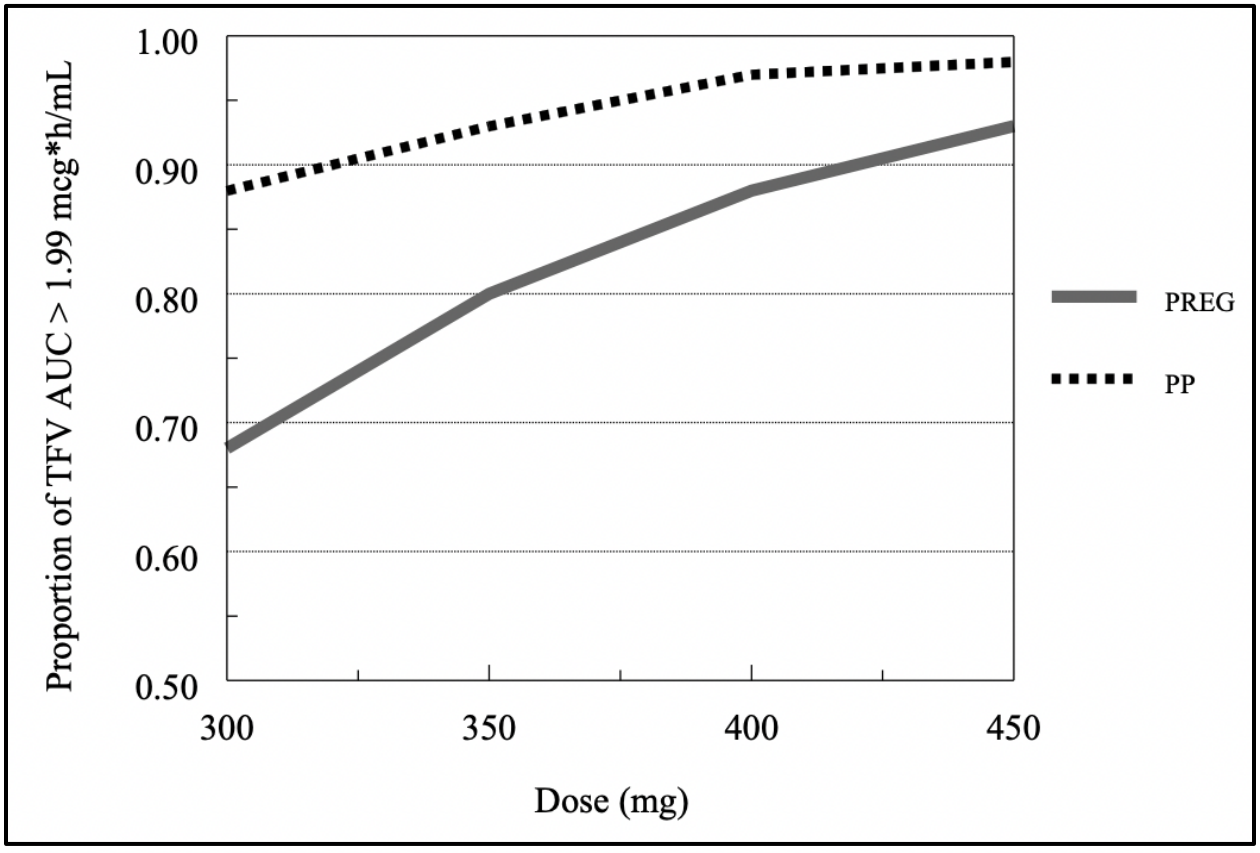
The median concentration versus time profiles for simulated pregnant and postpartum women are shown in ***Figure IIIk,*** and the proportion of TFV simulations in pregnant and postpartum women exceeding AUC >1.99 mcg*h/mL (the 10th percentile of the average exposure for non-pregnant historical controls)[4] are as shown in ***Figure IIIl***.

Figure IIIk: *Median tenofovir concentration versus time profiles for simulated pregnant and non-pregnant women, derived using the final population pharmacokinetic model. Solid lines represent lines of identity for pregnant women; while interrupted lines represent lines of identity for non-pregnant women.*



While pregnancy was not an independent covariate in the final POPPK model, the greater weight and lower serum creatinine that occurred during normal pregnancy resulted in a TFV profile during pregnancy that was lower throughout the dose interval than in postpartum women. This was associated a lower area under the concentration time curve (AUC) of 2.36 mcg*h/mL versus 3.02 mcg*h/mL, and higher CL/F of 57.6 L/h versus 44.9 L/h in simulated pregnant compared to postpartum women - ***Figure IIIk***. The probability of target attainment (exceeding AUC >1.99 mcg*h/mL) was 68%, 80%, 87%, and 93% above the target with 300mg, 350mg, 400mg and 450mg of TDF respectively in pregnant women, and 88%, 92%, 96% and 98% above the target with same doses in postpartum women, ***Figure IIIl***.

Figure IIIl: *Simulations of TFV proportion exceeding AUC >1.99 mcg*h/mL in pregnant (PREG) and postpartum (PP) women.*



DISCUSSION:

Using a population PK approach, we leveraged rich intensive TDF-derived TFV data to estimate individual PK parameters in pregnant women living with HIV. Among the investigated covariates, TFV CL/F and V_{ss}/F both increased with increasing gestation, which is consistent with previous reports of TFV PK during pregnancy.[4,8,9] The population PK parameters for TFV compared well with published values in the literature, and demonstrated that TFV CL/F is related to renal function, reflected as serum creatinine within the final model.[10,11,12]

A two-compartment model with first-order absorption and elimination, similar to the Hirt et al[7] and Benaboud et al,[8] best described the plasma concentrations of TFV in our study. Our POPPK model represents the first TDF-derived TFV pregnancy POPPK model from an intensive sampling (with paired evaluations – pregnancy and postpartum) of pregnant women living with HIV. This is important because the use of intensive PK and paired evaluations are advantageous, and can improve understanding of intra and inter-individual variability in PK parameter estimates needed for robust predictions.

Overall, the estimates for CL/F and V_1/F and the between subject variability compared well with previous studies. The population mean baseline V_1/F of 6.37 L/kg (446 L for a 70 kg pregnant woman) is similar to those reported (343–552 L) from other TDF-derived TFV pregnancy studies.[4,9] Furthermore, the overall variability (between subject and inter-occasion variability) of CL/F after accounting for variability in all covariates in our model was 35%. This variability in CL/F in our study was higher than the variability in the Hirt TFV intrapartum and postpartum model (CL/F of 30%), and lower than the overall variability in the Benaboud TFV model (CL/F

of 43%). One advantage of our population PK study is the separation of CL/F variability into inter-occasion (within subject) variability in CL/F and between subject variability in CL/F, a characteristic not reported and accounted for in other TDF-derived TFV pregnancy models. Accounting for within-subject variability in CL/F for TFV has advantages, as it explains some of the variability within-subjects that cannot be explained by between-subject variability. Other factors such as pharmacogenomic differences in single nucleotide polymorphisms (SNPs) in the genes coding for biotransformation and enzyme transport, drug-drug interactions, and other patient-specific covariates may also vary from one participant to the other and account for additional variability.

In our study, serum creatinine had a significant influence on TFV CL/F in the final population PK model. Therefore, we investigated the influence of renal function on TDF-derived TFV PK. Tenofovir has the potential to cause nephrotoxicity.[13] In fact, several studies demonstrate a mild to moderate decline in estimated glomerular filtration rate relative to baseline in patients taking TDF-based combination antiretroviral therapy.[14-16] Following oral administration of TDF, it is rapidly metabolized to TFV, which is then eliminated unchanged by a combination of glomerular filtration and active tubular secretion.[17,18] Approximately 70-80% of TDF-derived TFV is actively secreted from basolateral membranes of the kidneys into proximal renal tubular cells via the human organic anion transporter 1 (hOAT-1) and hOAT-3, and then extruded into the renal tubular lumen by the multidrug resistance transporter 2 (MRP-2) and MRP-4 luminal transmembrane transporters.[19,20] Therefore, increased accumulation of TFV in the renal tubular cells can potentially cause mitochondrial dysfunction and proximal tubular injury.[21,22] Thus, TDF fixed dose antiretroviral regimens should be used with caution in patients with renal insufficiency.[2] Our results showed that concomitant ritonavir use did not influence TFV PK, although decreased TFV

clearance has been previously reported in non-pregnant women.[23] While the inhibition of the MRP-2-mediated transport of TFV is a possible explanation for this PK interaction,[18] the physiologic changes in the renal system during pregnancy resulting in a decrease in plasma TFV concentrations might explain our findings.

When TDF is used during pregnancy, it is recommended that renal function testing be done at baseline, and then every six months, [1] the same schedule used for non-pregnant adults, and renally dose in patients with renal insufficiency. As TFV has limited plasma protein binding (<1% bound), changes in protein binding during pregnancy, which would in turn alter clearance via glomerular filtration, are not expected to alter TFV clearance. Instead, as TFV is principally renally cleared, physiologic changes of pregnancy likely to alter TFV serum concentrations would be related to renal function. During pregnancy, renal blood flow rises by about 70-80% from its baseline value at 20-22 weeks of gestation, peaks around 32-24 weeks of gestation, and then falls to about 60-70% above pre-pregnancy levels towards the end of pregnancy, while the glomerular filtration rate (GFR) rises in parallel by about 40-50% of its baseline values at 20-22 weeks, then continues to increase through most of the 3rd trimester (exceeding its baseline by about 50% at 36-38 weeks of gestation), then declines steadily until the time of delivery.[24-26] These pregnancy-related changes result in the mean serum creatinine of approximately 16%, 23% and 20% lower in the first, second and third trimesters of pregnancy compared to non-pregnant adults with normal kidney function.[27] The significant relationship between serum creatinine (a biomarker for renal function) and TFV CL/F in the final POPPK model is likely related to these renal changes during pregnancy.

Our findings using this POPPK model are biologically and pharmacologically plausible, and have important clinical implications. The results of TFV studies show that the efficacy of TDF-derived

TFV was highly variable among individuals, which could be related to plasma TFV exposure.[2] Morphologic and biological characteristics enabled us to explain some between subject variability of TFV PK parameters (24% for CL/F and 25% for V_{ss}/F), but these explain approximately half of clinical variability of TDF-derived TFV seen during pregnancy in our model. Although inter-occasion variability improves our understanding of TFV variability from this POPPK model by 26%, it cannot fully explain the variability in TDF-derived TFV exposure in pregnant women living with HIV. Other potential mechanisms, including variability in trans-membrane drug transporter mechanisms of TFV absorption, pharmaco-genomic variation in drug transporters, and drug metabolizing enzymes need to be explored. Our results show that TFV exposure decreased by 28% during pregnancy compared to postpartum. Examining known pharmacokinetic-pharmacodynamic (PKPD) relationships of TFV (AUC, viral response) in the context of lower exposures and what a clinically relevant decrease means in relation to these targets is critical during pregnancy. A prior TFV non-compartmental PK study reported that a 25 % decrease in TFV exposure was not associated with perinatal transmission or virologic failure.[9] In addition, our simulated TFV AUC in pregnant women of 2.36 mcg*h/mL is similar to TFV AUCs simulated from POPPK models in non-pregnant adults [2.62 mcg*h/mL,[28] 2.65 mcg*h/mL,[29] and 2.88[30] mcg*h/mL). Since TDF is available in 150mg (lowest dose) and 300-mg (standard dose) tablets, we simulated pregnant and postpartum AUCs following the administration of TDF in increments as follows: 300mg, 350mg, 400mg and 450mg of TDF. The probability of target attainment (proportion exceeding AUC of >1.99 mcg*h/mL, the 10th percentile of the average TFV exposure for non-pregnant historical controls),[4] was approximately 70% above this target with the standard dose (300mg) of TDF. It appeared that simulations of TDF doses ≥400mg during pregnancy and postpartum lead to very high serum concentrations of TFV. The probability of target attainment

simulations and the between subject variability in TFV clearance of 24% suggest that the standard 300mg of TDF is enough to reach target therapeutic thresholds for TFV during pregnancy and postpartum, and should not warrant TDF dose modifications during pregnancy. A pregnancy POPPK study in pregnant and postpartum women living with hepatitis B reported similar findings and recommendations.[31]

Our TFV pregnancy POPPK model has several strengths. First, our model described the PK of TFV with reasonable accuracy and precision in pregnant and postpartum patients. Second, our POPPK model examined the association between TFV concentrations and serum creatinine, which would be useful to optimize TDF dosing in pregnant women living with HIV with varying degrees of renal impairment. Third, we utilized rich, intensive PK sampling data for the POPPK model, which is precise and thorough enough to define accurately the metabolic phase of drug elimination of TDF-derived TFV. Fourth, we accounted for individual within subject variability PK parameters, including inter-occasion variability. Studies have shown that inter-occasion variability may change randomly between study occasions, and ignoring such inter-occasion variability may result in biased population parameter estimates, a high incidence of statistically significant spurious period effects, and a falsely optimistic impression of the potential value of therapeutic drug monitoring.[32]

Our study had limitations. We do not have first trimester PK data, so it was not possible to incorporate first trimester changes in TFV PK into our model. However, we do not think the lack of first trimester data had a substantial effect on our results because pregnancy physiology usually changes little in the first trimester. We did not collect data on TFV-DP, the active moiety of TFV,

so we could not investigate the relationship between plasma TDF-derived TFV and intracellular TFV-DP concentrations in our POPPK model. It would have been ideal to be able to predict intracellular TFV-DP concentrations, as the anti-retroviral activity of TDF is a function of intracellular TFV-DP levels.[12] The timing of TDF dose to meals was not controlled for in our POPPK model. Studies have demonstrated that TDF absorption is sensitive to high-fat diet, and differences in rate of absorption can account for PK differences in patients taking TDF, with K_a, C_{max} and AUC of TFV about 2-3 times higher in fed compared to fasted participants (25% bioavailability in the fasting state, and 39% bioavailability with a high-fat diet).[23]

In conclusion, the POPPK parameters of TDF-derived TFV in pregnant and postpartum women living with HIV was best described using a two-compartment model with first order absorption and elimination. Our model suggests that changes in TDF-derived TFV PK can be predicted by clinical factors and thus, any dose modifications for TFV during pregnancy and postpartum should be based on renal function and weight during the second and third trimesters of pregnancy, as well as postpartum. While weight and serum creatinine accounted for variability in CL/F unexplained by between-subject variability for CL/F (24%), these typical changes in BSV do not need dose adjustments in TDF during pregnancy and postpartum, but more extreme weights or renal function differences may warrant dose adjustments in pregnant and postpartum women. In situations where dose adjustments are warranted for TDF, switching to other antiretrovirals would also be another alternative. TDF is a cornerstone drug used in many anti-retroviral fixed dose combinations in pregnant women, and identification of other sources of variability would be vital to improving its safety and efficacy. Larger clinical studies with a range of doses exploring the impact of creatinine clearance and gene polymorphisms of TFV transporters would be critical.

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CHAPTER 4

Maternal and Fetal Outcomes in Pregnant Women Living with HIV on Tenofovir Disoproxil Fumarate compared to Tenofovir Alafenamide.

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Keywords:
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ABSTRACT:

Objective: Our objective was to assess the safety, efficacy, maternal and fetal outcomes of Tenofovir Disoproxil Fumarate (TDF) compared to Tenofovir Alafenamide (TAF) use in pregnant women living with HIV (PWLHIV).

Methods: This retrospective cohort study of all women who delivered at a single center (Johns Hopkins Hospital) between January 1st 2015 and June 30th, 2020 compared outcomes in PWLHIV using TDF compared to TAF. The primary outcome was weight gain during pregnancy. Secondary outcomes included serum creatinine concentrations, CD4 count, viral load, gestational age at delivery, fetal and neonatal outcomes. Demographics and outcomes were analyzed using standard statistical tests. Multivariable linear regression analysis models accounting for potential confounders were created for primary and secondary outcomes, with beta coefficients (β) and associated 95% confidence intervals as the primary measure of effect.

Results: There were 66 women in the TDF group and 34 women in the TAF group. In the overall cohort, the median (interquartile range, IQR) gestational age at delivery for PWLHIV on TDF and TAF were 38.6 (IQR 37.5-39.4) and 38.1 (31.1-39.1) weeks respectively; and most women (85%) were Black/African American. Compared to PWLHIV on a TDF regimen, women on TAF, on average, gained over 5kg more weight in the 3rd trimester of pregnancy (β = 5.20, 95% CI 1.64, 11.97; *p=0.03*). Women in the TAF arm were also more likely to have lower median serum creatinine concentrations (0.56 mg/dL versus 0.50 mg/dL, *p=0.048*) and a higher median CD4 count (470 cells/mm^3 versus 669 cells/mm^3, *p=0.035*) in the third trimester compared to women on TDF. There were no cases of neonatal/infant HIV, or death.

Conclusion: Although TAF use was associated with more weight gain compared to TDF, both regimens appear safe and effective during pregnancy. PWLHIV should be counseled about the potential for weight gain with TAF based regimens during pregnancy.

Key words: Tenofovir Disoproxil Fumarate; Tenofovir Alafenamide; Antiretroviral agents; HIV; AIDS; Pregnancy; Weight gain.

INTRODUCTION:

HIV infection in pregnancy continues to be of significant clinical and public health importance.[1,2] The current statistics published by the World Health Organization (WHO) demonstrate that 38 million people are living with HIV in 2019, and 1.1 million (85%) pregnant women living with HIV received antiretroviral therapy (ARVs) during pregnancy and postpartum.[1] Additionally, 53% of children living with HIV in 2019 are on lifelong ARVs.[1] Expectedly, remarkable progress has been made in preventing mother-to-child transmission of HIV during pregnancy and lactation, and management of pregnant women living with HIV has evolved significantly in the last three decades.[3,4]

Since the report of the first therapy for HIV in pregnant women living with HIV in 1994, significant improvements in highly active antiretroviral therapy (HAART) has revolutionized the management of HIV during pregnancy for maternal health and prevention of perinatal transmission.[2] These include the use of combination therapy with several newer ARVs, including integrase inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs).[5] While tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), two commonly used NRTI backbone in combination ARV, have similar efficacy, resistance profiles, and mechanisms of action (both prodrugs of tenofovir); they differ in their potency and adverse effect profiles.[2,4] Compared with TDF, TAF rapidly enters peripheral blood mononuclear cells (PBMCs) and other lymphoid tissues following ingestion, resulting in approximately 90% decreased plasma tenofovir (TFV) concentrations.[6] This pharmacokinetic (PK) characteristic increases the potency and antiviral activity of TAF, and decreases the potential for adverse effects from TAF compared to TDF.[2] From a pharmacodynamic (PD) perspective, TAF's median TFV concentrations exceeds its 90%

effective concentration (EC_{90}) 1–2 hours after a single dose, whereas TDF does not exceed this threshold until after approximately 3 days of daily dosing.[7] These pharmacokinetic pharmacodynamic (PKPD) characteristics of TAF may be advantageous in pregnancy for rapid decline in HIV viral load to prevent perinatal transmission. Despite these advantages, TAF is not currently recommended in pregnancy for perinatal transmission due to its limited PK and safety data,[2] and the clinical impact of these differences between TDF and TAF has not been fully studied during pregnancy.

While TDF and TAF have been studied extensively in non-pregnant populations from a pharmaco-epidemiologic perspective,[8-15] there are limited studies of TAF use during pregnancy[16,17] despite the increasing use of TAF fixed dose combination ARVs during pregnancy for treatment of maternal HIV infection and for prevention of perinatal transmission. To date, TDF data in pregnancy has been reassuring, as the Promoting Maternal Infant Survival Everywhere (PROMISE) randomized clinical trial did not identify associations between high TDF exposure, as measured by maternal tenofovir diphosphate (TFV-DP) concentrations in dried blood swabs, and adverse maternal, fetal and neonatal outcomes.[18] Although TAF use in non-pregnant adults has been associated with weight gain and metabolic syndrome,[19,20] only one study has evaluated the maternal and fetal outcomes in pregnant and postpartum women living with HIV on TAF compared to TDF.[21] Data from TAF and TDF pharmacoepidemiologic pregnancy studies are critical because the effectiveness of ARV therapy has to be considered alongside the potential for maternal adverse effects and the risk for congenital anomalies in fetuses of pregnant women living with HIV.

Therefore, the objective of this study was to assess the safety, efficacy, maternal and fetal outcomes of Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF) use in pregnant women living with HIV (PWLHIV).

MATERIALS AND METHODS:

This was a retrospective cohort study of all cases of pregnant women living with HIV at the Johns Hopkins Hospital HIV in pregnancy (HALO) clinic between January 1st, 2015 and June 30th, 2020 (5 and half year period). The cohort included pregnant women living with HIV aged 18 to 48 years of age, at ≥ 6 0/7 weeks of gestation and their HIV-exposed neonates. Pregnant women met criteria for inclusion if they used a TDF based regimen [TDF, emtricitabine (*Truvada*); TDF, emtricitabine, efavirenz (*Atripla*); TDF, emtricitabine, rilpivirine (*Complera*); TDF, emtricitabine, elvitegravir, cobicistat (*Stribild*)]; or a TAF based regimen [TAF, emtricitabine (*Descovy*); TAF, emtricitabine, rilpivirine (*Odefsey*); TAF, emtricitabine, elvitegravir, cobicistat (*Genvoya*); TAF, emtricitabine, darunavir, cobicistat (*Symtuza*); TAF, emtricitabine, dolutegravir; and TAF, emtricitabine, bictegravir (*Biktarvy*)] during pregnancy and postpartum. Women were described as ARV naïve (initiators) if they started taking these ARVs (TDF or TAF) for the first time during pregnancy, or ARV experienced if they had previously been on a TDF or TAF regimen before pregnancy, and continued during pregnancy.

Demographic data, medical history, laboratory testing of mother and infant pairs were collected via chart review and recorded on a standardized form. Data extracted included maternal age; parity; ethnicity; gestational age at enrolment; gestational age at delivery; maternal weight in the first, second and third trimesters of pregnancy; viral load in the first, second and third trimesters of

pregnancy; CD4 counts in the first, second and third trimesters of pregnancy; serum creatinine in the first, second and third trimesters of pregnancy; history of alcohol, cocaine, tobacco or heroin use prior to pregnancy; methadone use during pregnancy; hypertension during pregnancy; gestational diabetes mellitus; preterm delivery; Hepatitis B and/or Hepatitis C co-infection during pregnancy; and mode of delivery. Fetal and neonatal outcomes included intrauterine fetal death, the presence of fetal anomalies, birth weight, low birth weight (birth weight <2500 grams), and neonatal death. The exposure of interest was TDF or TAF use, and the primary outcome was maternal weight gain during pregnancy. The secondary outcomes included all other maternal and fetal outcomes. Institutional Review Board (IRB) approval was completed prior to the study.

Statistical analysis:

The first step in our analysis was exploratory data analysis. We used diagrammatic methods (frequency distributions) to check our data for missing variables, check assumptions, identify outliers and influential observations, determine relationships among the explanatory variables, and assess the direction and approximate size of relationships between explanatory and outcome variables. Descriptive analyses were then performed to describe the study sample. We compared sociodemographic and clinical characteristics, and determined their frequency between the exposure groups (TDF versus TAF). Categorical variables were reported as proportions, and continuous measures were reported as medians as described in ***Tables IVa*** *and* ***IVb***. Differences between groups were assessed with Fisher's exact tests and Chi-square test for categorical variables (where applicable), and Student's t-tests for continuous variables.

Linear regression models were used to estimate beta coefficients (β) with their associated 95% confidence intervals, accounting for potential confounders – ***Table IVc***. β regression coefficients indicate how much a dependent variable changes per unit variation of the independent variable, taking into account the other independent variables in the model. For categorical variables (e.g. TDF vs TAF use (TDF=0, TAF=1); nulliparity vs multiparity (nulliparity=0, multiparity=1); no diabetes vs diabetes (no diabetes=0, diabetes=1); and no hypertension versus hypertension (no hypertension=0, hypertension=1), the β coefficient represents the effect of moving from the "reference category" (coded as 0) to another category (coded as 1). We assessed model fit and parsimony using Akaike's Information Criteria (AIC). All statistical analyses were conducted in Stata, version 15.1 (StataCorp, College Station, TX; 2019).

RESULTS:

Table IVa show characteristics of the study population, stratified by NRTI backbone (TDF versus TAF). A total of 100 women were studied (66 women on a TDF based fixed dose combination, and 34 women on a TAF based combination). Pregnant women living with HIV on a TDF regimen were older than those in the TAF arm (median age of 32 years (interquartile range, IQR (29-36) in the TDF group and 29 years (IQR 25-32) in the TAF group; p value= *0.045*). Women were evenly split by nulliparity (9 women each in the TDF and TAF arms), compared to the multiparous arms, *p=0.246*). Gestational age at enrolment (median 14.2 weeks (IQR 11.3-19.6) in the TDF group versus 12.4 weeks (IQR 9.6-16.0) in the TAF group; *p=0.264*) and gestational age at delivery (median 38.6 weeks (IQR 37.5-39.4) in the TDF arm versus 38.1 weeks (IQR 37.1-39.1) in the TAF arm; *p=0.203*) were similar. The majority of participants were Black or African Americans [54/66 (82 %) in the TDF group and 31/34 (91%) in the TAF group, p value= *0.115*)].

Table IVa: Maternal Demographics for pregnant women on TDF versus TAF.

Variable	Tenofovir Disoproxil Fumarate (TDF) N=66	Tenofovir Alafenamide (TAF) N=34	P-value
Age (median in years; *IQR*)	32 (29-36)	29 (25-32))	0.045
Parity, *n (%)*			
Para 0	9 (14)	9 (27)	0.246
Para 1	23 (35)	11 (32)	
Para 2	20 (30)	11 (32)	
Para 3 or greater	14 (21)	3 (9)	
Gestational age at enrolment, *median (IQR)*	14.2 (11.3-19.6)	12.4 (9.6-16.0)	0.264
Gestational age at delivery, *median (IQR)*	38.6 (37.5-39.4)	38.1 (37.1, 39.1)	0.203
Race, *n (%)*			
Black/African American	54 (82)	31 (91)	0.115
Caucasian	8 (12)	0 (0)	
Hispanic	3 (5)	1 (3)	
Others	1 (1)	2 (6)	
Weight (kg), *median, IQR*			
1st trimester	81.1 (66.7-98.4)	81.1 (68.1-101.2)	0.931
2nd trimester	81.6 (70-99.3)	81.2 (69.7-103.8)	0.967
3rd trimester	87.1 (77.2-100.8)	92.1 (79.8-108.9)	0.042
Weight gain (kg), *median, IQR*			
2nd trimester	2.75 (0.9-4.5)	3.0 (1.1-5.1)	0.554
3rd trimester	3.75 (1.0-7.7)	6.2 (2.7-13.6)	0.036
Number of mothers with viral load <20 copies/mL, *n, (%)*			
1st trimester	48 (73)	25 (74)	0.964
2nd trimester	54 (82)	28 (82)	0.854
3rd trimester	55 (84)	29 (86)	0.791
CD4+ (cells/mm^3), *median, IQR*			
1st trimester	569 (373-766)	667 (512-973)	0.050
2nd trimester	444 (353-620)	510 (420-722)	0.230
3rd trimester	470 (355-594)	669 (514-750)	0.035
Serum creatinine (mg/dL), *median, IQR*			
1st trimester	0.6 (0.5-0.7)	0.6 (0.4-0.6)	0.725
2nd trimester	0.59 (0.51-0.62)	0.57 (0.5-0.6)	0.598
3rd trimester	0.56 (0.5-0.7)	0.50 (0.4-0.7)	0.048
Alcohol use prior to pregnancy, *n (%)*	1 (2)	2 (5)	0.980
Cocaine use prior to pregnancy, *n (%)*	5 (8)	0 (0)	0.100
Heroin use prior to pregnancy, *n (%)*	2 (3)	1 (3)	0.980
Methadone use in pregnancy, *n (%)*	3 (5)	2 (6)	0.771
Tobacco use prior to pregnancy, *n (%)*	6 (9)	7 (20)	0.105
Hypertension during pregnancy, *n (%)*	5 (8)	3 (9)	0.127
Gestational diabetes mellitus, *n (%)*	2 (3)	2 (6)	0.201
Preterm delivery, *n (%)*	9 (14)	3 (9)	0.496
Hepatitis B, *n (%)*	1 (2)	1 (3)	0.629
Hepatitis C, *n (%)*	3 (5)	0 (0)	0.207
Mode of delivery *(n (%)*			
Vaginal delivery	41 (62)	17 (50)	0.212
Cesarean delivery	25 (38)	17 (50)	
Cesarean delivery for viral load, *n (%)*	4 (6)	0 (0)	0.083

Maternal weight in the first and second trimesters of pregnancy were similar between women on TDF compared to those on TAF (median 81.1 kg (IQR 66.7-98.4) in the TDF arm versus 81.1 kg (IQR 68.1-101.2) in the TAF arm; *p=0.931* in the first trimester; and 81.6 kg (IQR 70-99.3) in the TDF arm versus 81.2 kg (IQR 69.7-103.8) in the TAF arm in the second trimester, *p=0.967*). Women in the TAF arm were more likely to weight more in the third trimester compared to women on TDF (87.1 kg (IQR 77.2-100.8) in the TDF arm versus 92.1 kg (IQR 79.8-108.9) in the TAF arm; *p=0.042*). Compared to women on TDF, women on a TAF based regimen had a higher weight gain during the third trimester of pregnancy [3.75kg (1.0-7.7) on TDF versus 6.2kg (2.7-13.6) on TAF; p=*0.036*]. 48/66 (73%) of women on TDF versus 25/34 (74%) of women on TAF had viral loads <20 copies/mL (*p=0.964*) in the first trimester; 54/66 (82%) of women on TDF versus 28/34 (82%) of women on TAF had viral loads <20 copies/mL (*p=0.854*) in the second trimester, and 55/66 (84%) of women on TDF versus 29/34 (86%) of women on TAF had viral loads <20 copies/mL (*p=0.791*) in the third trimester of pregnancy. Women on TAF were more likely than those on a TDF regimen to have a higher CD4 count (median 470 cells/mm^3 (IQR 355-594) in the TDF arm versus 669 cells/mm^3 (514-750); *p=0.035*) in the third trimester of pregnancy.

Median maternal serum creatinine concentrations in the first and second trimesters of pregnancy were similar between women on TDF compared to those on TAF [(0.6 mg/dL (IQR 0.5-0.7) in the TDF arm versus 0.6 mg/dL (IQR 0.4-0.6) in the TAF arm; *p=0.725*] in the first trimester; and 0.59 mg/dL (IQR 0.51-0.62) in the TDF arm versus 0.57 mg/dL (IQR 0.5-0.6) in the TAF arm in the second trimester; *p=0.598*). Women in the TAF arm were more likely to have lower serum creatinine concentrations in the third trimester compared to women on TDF (0.56 mg/dL (IQR 0.5-0.7) in the TDF arm versus 0.5 mg/dL (0.4-0.7) in the TAF arm, *p=0.048*). There were no

significant differences between women on TDF and those on TAF with respect to alcohol, cocaine, heroin, methadone, and tobacco use; hypertension in pregnancy, preterm delivery, hepatitis B and C infections, and mode of delivery. Four women in the TDF arm (6%) were delivered by Cesarean for viral loads >1,000 copies/mL, while none was delivered in the TAF arm solely for a high viral load indication. All women in this study reported >90% medication adherence.

Table IVb shows the fetal and neonatal characteristics in this study population stratified by NRTI backbone (TDF versus TAF). There were no statistically significant differences between women taking TDF versus TAF with respect to birth weight (median neonatal weight of 3230 grams (IQR 2480-3520) in the TDF arm versus 3150 grams (IQR 2580-3495) in the TAF, *p=0.260*), intrauterine fetal death, fetal anatomic abnormalities, low birth weight, and neonatal death. None of the infants of the mothers on TDF or TAF were HIV infected. 5/66 fetuses (8%) in the TDF arm and 3/34 fetuses (9%) in the TAF arm had a diagnosis of some fetal anatomic anomalies during pregnancy and postpartum, including mild urinary tract dilatation (two fetuses), unilateral postaxial polydactyly (two fetuses), fetal dangling choroid (one fetus), left supernumerary nipple (one fetus), urachal cyst (one fetus), and right talipes equinovarus (one fetus).

Table IVb: Fetal and Neonatal outcomes for pregnant women on TDF versus TAF

Variable	Tenofovir Disoproxil Fumarate (TDF) N=66	Tenofovir Alafenamide (TAF) N=34	P-value
Intrauterine fetal death, *n (%)*	1 (2)	1 (3)	0.638
Fetal anatomic anomalies, *n (%)*	5 (8)	3 (9)	0.932
Birth weight (grams), *median (IQR)*	3230 (2480-3520)	3150 (2580-3495)	0.260
Low birth weight (Birth weight <2500 grams)	4 (6)	3 (9)	0.145
Infant infection status Uninfected by best available data, *n (%)*	66 (100)	34 (100)	-
Neonatal death, *n (%)*	0 (0)	(0)	-

IQR – Interquartile range

Table IVc shows the univariable and multivariable linear regression analysis of the associations between TDF and TAF use and a number of covariates. In the univariable analysis using logistic regression, pregnant women living with HIV on a TAF regimen, on average, gained 6.8kg more weight during the 3rd trimester of pregnancy compared to those on TDF (β = 6.80, 95% CI 1.46, 13.14; *p=0.04*)). TAF use was also associated with decreased serum creatinine concentrations (β = -0.05, 95% CI 0.11, -0.002; *p=0.03*) compared to those on TDF. In the multivariable linear regression model, pregnant women living with HIV on a TAF regimen, on average, gained 5.2kg more weight during the 3rd trimester of pregnancy compared to those on TDF (β = 5.20, 95% CI 1.64, 11.97; *p=0.03*), and remained statistically significant as described in ***Table IVc***. The remainder of the maternal covariates were not statistically significant.

Table IVc: Univariable and multivariable regression model

	Univariable linear regression			**Multivariable linear regression**		
Outcome: Maternal weight gain in the 3rd trimester	Beta Regression coefficient	95% CI	P-value	Beta Regression coefficient	95% CI	P-value
TAF use	6.80	1.46, 13.14	**0.04**	5.20	1.64, 11.97	**0.03**
Maternal age	-0.28	-0.79, 0.23	0.27	-0.11	-0.66, 0.43	0.68
Gestational age	-0.67	-1.38, 0.04	0.06	-0.35	-1.10, 0.41	0.36
Parity	-2.87	-5.89, 0.14	0.27	-1.91	-5.05, 1.23	0.23
Diabetes	-1.87	-21.9, 18.16	0.86	-1.96	-23.0, 19.08	0.85
Outcome: Serum creatinine in the 3rd trimester	Beta Regression coefficient	95% CI	P-value		95% CI	P-value
TAF use	-0.05	-0.11, -0.002	**0.03**	-0.06	-0.12, 0.003	0.07
Maternal age	0.003	-0.001, 0.007	0.17	0.002	-0.003, 0.006	0.47
Maternal weight, 3rd trimester	0.0002	-0.001, 0.001	0.76	0.0007	-0.0005, 0.02	0.26
Hypertension	0.014	-0.09, 0.115	0.78	-0.07	-0.19, 0.06	0.30
Gestational age	0.005	-0.001, 0.011	0.12	0.003	-0.003, 0.01	0.34
Diabetes	0.116	-0.07, 0.30	0.21	0.22	-0.009, 0.45	0.06

**β regression coefficients indicate how much a dependent variable changes per unit variation of the independent variable, taking into account the other independent variables in the model. For categorical variables (e.g. TDF vs TAF use (TDF=0, TAF=1); nulliparity vs multiparity (nulliparity=0, multiparity=1); no diabetes vs diabetes (no diabetes=0, diabetes=1); and no hypertension versus hypertension (no hypertension=0, hypertension=1), the β coefficient represents the effect of moving from the "reference category" (coded as 0) to another (coded as 1).*

DISCUSSION:

We found that pregnant women living with HIV and on a TAF regimen, on average, gained 5.2kg more weight during the 3rd trimester of pregnancy compared to those on TDF. While TAF use was associated with decreased serum creatinine concentrations, especially in the third trimester of pregnancy, this was not statistically significant in the multivariable analysis. There were no cases of perinatal transmission of HIV or neonatal death in this cohort.

The increased serum progesterone concentrations, as well as other physiologic changes during pregnancy, lead to increased maternal weight, especially in the third trimester of pregnancy.[22,23] The physiologic weight gain during pregnancy is usually within the recommendations set by the Institute of Medicine (IOM) during pregnancy for optimal maternal and fetal outcomes,[24] because weight gain in excess of those recommended by the IOM can be associated with adverse maternal and neonatal outcomes.[25,26] In this study, we reported that pregnant women living with HIV on a TAF regimen, on average, gained 5.2kg more weight during the 3rd trimester of pregnancy compared to those on TDF. The association between TAF-based regimens and weight gain (when compared to TDF), has been demonstrated in several randomized clinical trials, including the ADVANCE[19] and AMBER[20] randomized controlled trial in non-pregnant adults, and the VESTED trial[21] in pregnant women. These clinical trials demonstrate significant differences in weight gain when comparing TAF based regimens to other ARVs. Data from the ADVANCE trial demonstrated that weight gain in non-pregnant women using a TAF based regimen was approximately 3kg greater than the weight gain in men (6 kg weight gain in men versus 9 kg weight gain in women).[19] While the explanation for TAF-associated weight gain in non-pregnant adults stem from several risk factors like a 'return to health' effect in those with weight loss due to HIV

and its complications, low pretreatment CD4 cell count, high viral load, Black race, genetic differences in metabolism of ARVs and their effects on weight gain, female sex,[27] and differences in baseline weight;[28] the causes of TAF-associated weight gain during pregnancy are unknown. Similarly, the clinical consequences and mechanisms that induce these differences in weight between TDF and TAF users during pregnancy remain unknown. Although there is evidence from the DISCOVER randomized clinical trial[7] that TDF may have inhibitory effects on weight gain, which might explain some of the weight differences observed when TDF and TAF based regimens are compared,[7] pregnant women were excluded from the DISCOVER randomized clinical trial, so it is difficult to extrapolate the findings from the DISCOVER trial to pregnant women. Understanding the clinical consequences of TAF-induced weight gain, and how it is modified during pregnancy by covariates like maternal age, gestational age, parity, race and other maternal and fetal factors are critical research questions, especially in women with class III obesity (body mass index of $\geq$40 kg/m^2).

Results of this study demonstrated that fetal anatomic anomalies were present in 5 fetuses (8%) of women on a TDF based regimen and 3 (9%) of patients on TAF based regimen. These fetal anomalies are minor, with no clinical significance, and unlikely related to TAF or TDF use during pregnancy because there were no specific organ malformation patterns identified. Therefore, a clear causal association between use of TAF or TDF and fetal anomalies cannot be established. While there is a dose-response relationship between most drugs and the risk of adverse effects and congenital anomalies,[29-31] TDF exposure during pregnancy has been associated with reduced neonatal whole-body bone mineral density, decreased mean length-for-age Z-scores, and lower head circumference-for-age Z scores at one year of age in children enrolled in the Surveillance

Monitoring for ART Toxicities (SMARTT) cohort study,[32] but these findings were most likely of uncertain significance. TAF results in lower systemic concentrations of TFV, and produces higher intracellular concentrations of TFV-DP than TDF. It remains uncertain if higher intracellular TFV-DP concentrations would increase the risk of congenital anomalies and adverse pregnancy outcomes. The HIV Antiretroviral Pregnancy Registry (APR), a project established in 1989 to monitor prenatal ARV exposures and detect potential increases in the risk of teratogenicity, keeps record of fetal anomalies resulting from all ARVs used in pregnant women.[33] Although ARV information from the APR continues to increase, there remains a paucity of data on TAF use during pregnancy. In the IMPAACT P1026s TAF 25 mg and 10 mg boosted with cobicistat study arms,[16] congenital anomalies considered possibly related to study drugs included a ventral septal defect (VSD) in one infant and congenital pseudo-arthrosis of the left clavicle and neonatal compartment syndrome in another infant. Data from this study and other IMPAACT P1026s studies involved a small number of women receiving TAF based regimens, so it is difficult to conclude that these congenital anomalies were related to TAF or other ARVs in the fixed dose combinations, or if they were incidental findings. In addition, the number of cases related to TAF reported in the APR at this time is insufficient to draw any reasonable conclusions on the association between TAF and any congenital anomalies at the current time. As more data become available, additional information on possible adverse effects and risk of teratogenicity will be gathered.

TAF and TDF based regimens have similar virologic efficacy. However, several studies have demonstrated that compared with TDF based regimens, TAF based regimens have fewer TFV associated adverse effects, such as proximal renal tubular toxicity and reductions in bone mineral density.[34-36] While TAF use in our study was associated with decreased serum creatinine

concentrations, this was not statistically significant in the final multivariable model. High serum levels of TFV has the potential to cause nephrotoxicity.[4] In fact, several studies demonstrate a mild to moderate decline in estimated glomerular filtration rate (GFR) relative to baseline in patients taking TDF-based combination ARVs,[37-39] with improvement of renal function after a switch from TDF to TAF.[35] Approximately 70-80% of TDF-derived TFV is actively secreted from basolateral membranes of the kidneys into proximal renal tubular cells via the human organic anion transporter 1 (hOAT-1) and hOAT-3, and then extruded into the renal tubular lumen by the multidrug resistance transporter 2 (MRP-2) and MRP-4 luminal transmembrane transporters.[40,41] Therefore, increased accumulation of TFV in the renal tubular cells can potentially cause mitochondrial dysfunction and proximal tubular injury. The physiological increase in GFR during pregnancy (by about 40-50% of its baseline values at 20-22 weeks) might explain why TFV did not accumulate in toxic concentrations to cause renal injury in our cohort, as increased blood flow and GFR during pregnancy increases drug and metabolite clearance from the kidneys. But if proximal tubulopathy develops in a pregnant women on a TDF based regimen, a reasonable alternative would be to switch to a TAF based regimen to prevent progression to chronic kidney disease. However, it is important to exclude other common causes of kidney dysfunction during pregnancy, like pre-eclampsia with severe features and hemolytic uremic syndrome before such a switch is made. For individuals with proximal tubulopathy and progressive kidney dysfunction during pregnancy, TFV (both as TDF or TAF) should be avoided, especially if the GFR falls below 50 mL/min/1.73 m^2.

One of the limitations of this study is the inability to distinguish weight gain attributable to dolutegravir (DTG) versus TAF when drug combinations of DTG/TAF are used in pregnant women. In the ADVANCE and VESTED trial data that randomized participants to TAF/DTG (arm

1), TDF/DTG (arm 2), and TDF/Efavirenz (arm 3), there was increased weight in participants randomized to the TAF/DTG and TDF/DTG arms. However, because women randomized to the TAF/DTG arm had the highest weight gain, it is plausible that TAF and DTG contributed to the increased weight, but it is unknown to what extent TAF and/or DTG increased maternal weight. Another potential limitation of this study is the relatively small sample size to enable analysis by sub-groups. With an increased sample size, it may have been possible to show statistically significant differences in serum creatinine concentrations between women who used TDF compared to TAF during pregnancy. Lastly, while all women in this study reported >90% medication adherence, there was no objective way to ascertain adherence to TDF/TAF medications in this study. This is important because non-pharmacologic adherence measures, such as patient self-report, calculation of proportion of pill days covered, pillbox checks, and use of electronic pill boxes/apps, have limitations and may overestimate or underestimate ARV adherence.[2,42]

Strengths of this study include the relatively high number of pregnant women living with HIV managed at this single center - greater than what is seen in many institutions in the United States. Furthermore, while TAF is not currently used in the management of pregnant women living with HIV in most institutions within and outside the US, its use during pregnancy for care of pregnant women living with HIV at this institution enabled us to complete this study. Additionally, given that TAF use in this study was part of routine obstetric care (and outside of a research protocol), the results may be more generalizable to more obstetric practices.

In summary, we found that although TAF use was associated with more weight gain compared to TDF, both regimens appear safe and effective during pregnancy. Pregnant women living with HIV

should be counseled about the potential for weight gain with TAF based regimens during pregnancy, especially in the third trimester, as well as and behavior modifications to mitigate weight gain with TAF based regimens.

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CHAPTER 5

OVERALL THESIS CONCLUSIONS:

The three projects in this thesis evaluated several critical aspects of ARVs, with the overall goal of optimizing HIV therapeutics for pregnant and postpartum women living with HIV.

In **Chapter 2**, we conducted a prospective phase IV study of the PK and safety of darunavir/ritonavir in pregnant and postpartum women living with HIV, and hypothesized that increased dose darunavir (800/100 twice daily) during pregnancy would increase darunavir plasma exposure to levels similar to those seen in non-pregnant women. In two previous pregnancy PK studies,[1,2] darunavir/ritonavir plasma concentrations were decreased. Darunavir exposure with 800mg/100mg once daily dosing was reduced by 38% during the second trimester and by 39% during the third trimester, while with 600mg/100mg twice daily dosing, darunavir plasma concentrations was reduced by 26% in both trimesters.[2] Similarly, increasing the darunavir/ritonavir dose to 800mg/100 mg twice daily during pregnancy in this study failed to significantly increase darunavir exposure compared to 600mg/100mg twice daily throughout pregnancy and postpartum (as darunavir 800mg/100mg BID was associated with a 38% reduction during the second trimester and 34% reduction during the third trimester of pregnancy compared to postpartum). This is in contrast to findings with other protease inhibitors like atazanavir, lopinavir and nelfinavir, where increased dosing during pregnancy improved drug exposure.[3-6] While viral suppression was fairly good in the participants in this study, if achieving darunavir exposure during pregnancy equivalent to that in non-pregnant adults is desired, other strategies, such as increasing the ritonavir dose should be investigated.

In **Chapter 3**, we sought to understand between-subject and within-subject factors like maternal age, weight, race, parity, creatinine clearance, and other physiologic parameters[7,8] that influence changes in TFV exposure patterns in pregnant and postpartum women living with HIV, by conducting a population pharmacokinetic study of TFV, in order to recommend appropriate TFV dosing (when used as TDF) during pregnancy. Changes in apparent clearance of TFV was only associated with enhanced renal function (as TFV apparent clearance was 28% higher during pregnancy compared to postpartum). Probability of target attainment analysis comparing plasma exposure of TFV against a target TFV exposure area under the curve of ≥1.99 mcg•hr/mL (the 10th percentile of average TFV exposure for non-pregnant historical controls)[9] demonstrated that dose adjustment of TDF during pregnancy is not generally warranted. However, any modification in dosing during pregnancy should be based on maternal renal function. TDF is a cornerstone drug used in many ARV fixed dose combinations in pregnant women, and identification of other sources of variability would be vital to improving its safety and efficacy. Future larger clinical studies with a range of doses exploring the impact of creatinine clearance and gene polymorphisms of TFV drug transporters, would be critical.

In **Chapter 4**, we conducted a retrospective cohort study of all pregnant women living with HIV on a TFV based regimen (TDF or TAF) at the Johns Hopkins Hospital to assess drug safety and efficacy in pregnant women living with HIV and their fetuses. While TDF and TAF, two commonly used nucleoside reverse transcriptase inhibitor (NRTI) backbone in combination ARV, have similar efficacy, resistance profiles, and mechanisms of action (both prodrugs of TFV), they differ in their potency and adverse effect profiles.[10,11] We demonstrated that pregnant women living with HIV on a TAF regimen, on average, gained 5.2kg more weight during the 3rd trimester

of pregnancy compared to those on TDF. There were no cases of neonatal/infant HIV or death. The findings from this study suggest that although TAF use was associated with more weight gain compared to TDF, both regimens appear safe and effective during pregnancy. It becomes imperative that pregnant women living with HIV should be counseled about the potential for weight gain with TAF based regimens during pregnancy. In addition, future studies should focus on understanding the etiologies and clinical consequences of TAF-associated weight gain, as well as the mechanisms that induce these differences in weight between TDF and TAF during pregnancy.

In **Conclusion**, several knowledge gaps still remain in understanding the pharmacology of new HIV drugs, physiologic changes affecting drug disposition, and drug safety in pregnancy that prevent efficient and effective deployment of our most promising new HIV drugs in pregnant women. My research in the next 3-5 years will focus on understanding the areas of ARV use in pregnant and postpartum women described below (A-D):

A. ***Use of TAF during pregnancy and the risk of metabolic syndrome:***

Given the recent data pointing toward weight gain concerns with TAF-based drugs in pregnancy, TAF use during pregnancy and the potential for metabolic changes need to be examined. Pregnancy is known to be associated with weight gain, especially during the second and third trimesters. It is unknown whether TAF use in pregnancy would predispose to an increased risk for metabolic syndrome, which could increase adverse pregnancy outcomes in the short and long term. Understanding whether TAF-induced metabolic syndrome is modified during pregnancy by age, gestational age, parity, and race are critical research questions, especially in women with class III

obesity (body mass index of ≥40 kg/m^2). Answers to these questions are necessary before we can be confident that TAF can be used safely and effectively in pregnant women.

B. ***Intracellular TFV-DP data in pregnancy are limited:***

TAF and TDF are phosphorylated by intracellular kinases to tenofovir-monophosphate (TFV-MP), and then to their active metabolite, TFV-DP after oral administration and absorption. However, intracellular TFV-DP data during pregnancy are currently limited to dried blood swab (DBS) assessments with only TDF. The Promoting Maternal Infant Survival Everywhere (PROMISE)[12] randomized clinical trial did not identify associations between higher TDF exposure, as measured by maternal TFV-DP concentrations in DBS, and adverse maternal, fetal and neonatal outcomes.[12] Several studies have consistently demonstrated lower plasma TFV and higher intracellular TFV-DP concentrations in PBMCs in non-pregnant adults on TAF-based regimens compared to TDF.[13-17] However, there are currently no data describing TFV-DP intracellular levels within PBMCs in pregnant, postpartum and lactating women on TAF. These assessments are planned in IMPAACT 2026.

C. ***There are currently no TAF population PK and PBPK studies in pregnant women:***

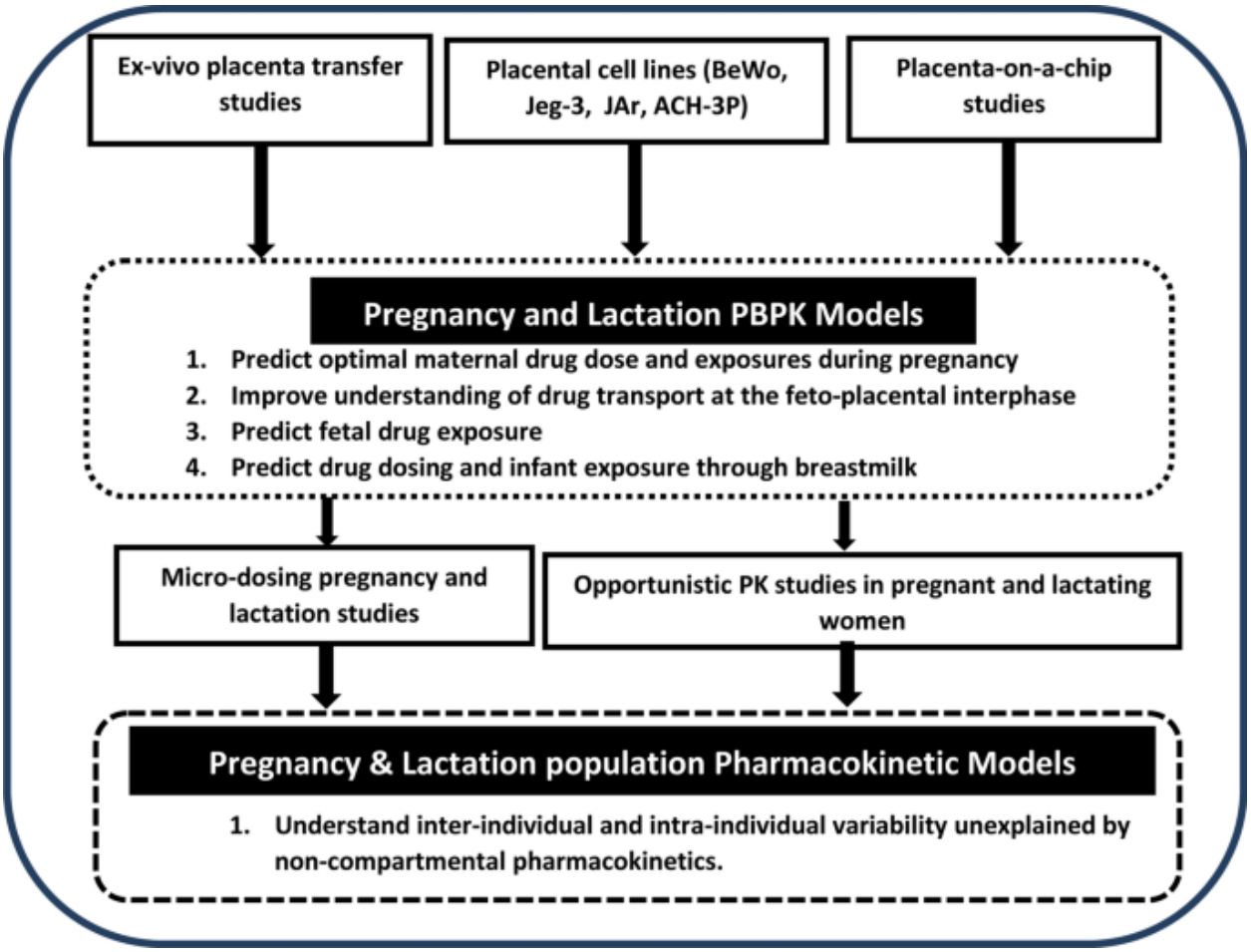
Population PK of TAF use during pregnancy has not been described, as current TAF population PK models exclude pregnant women. A future population PK study of TAF disposition during pregnancy, with appropriate covariate–parameter relationships and covariate stratification, would be critically important to the prediction of TAF disposition across the different trimesters of pregnancy and postpartum. Gestational changes in placental drug transporter expression and activity remain an area of intense study,[18] yet very little is known regarding their regulation during

pregnancy. To address limitations of population PK in predicting in utero drug exposures, data on the expression of drug transporters in the placenta in combination with cord blood samples at birth could be incorporated into physiologically-based pharmacokinetic (PBPK) models - ***Figure V***. It is of critical importance to further understand the role of placental P-gp, BCRP, as well as other drug transporters in regulating TAF, TFV and TFV-DP transfer to the developing fetus, and how these transporter functions are altered during pregnancy.

D. Unmet need for objective quantitative measures of adherence for TAF during pregnancy:

There remains a critical, unmet need for objective, quantitative measures of ARV adherence and drug levels at the site of action (i.e., PBMCs) among women living with HIV in pregnancy. Non-pharmacologic adherence measures, such as patient self-report, calculation of proportion of pill days covered, pillbox checks, and use of electronic pill boxes/apps, have limitations and may over-estimate or underestimate ARV adherence.[19] To address these shortcomings, multiple pharmacologic adherence measures have been developed to objectively quantify ARV medication adherence,[18,19] with TFV-DP levels in PBMCs being the most exciting.[20,21] However, there are currently no data on TAF TFV-DP concentrations in PBMCs during pregnancy. Examining TFV-DP concentrations in PBMCs will provide critical insights as to whether changes in plasma levels of TAF or TFV result in clinically relevant changes in TFV-DP levels at the site of action. Assessments of intracellular TFV-DP levels in PBMCs with TAF during pregnancy are developments likely to be clinically important in the future for understanding relationships with medication adherence and drug levels at the site of action.

Figure V: *Overview of innovative approaches to studying drug disposition in pregnancy and lactation. PK- pharmacokinetic; PBPK – physiologically based pharmacokinetic.*



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PUBLICATIONS:

Original Research:

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74. Broni EK, **Eke AC**, Vaidya D, Tao X, Northington FJ, Everett AD, Graham EM. Blood biomarkers for neonatal hypoxic ischemic encephalopathy in the presence and absence of sentinel events. J Perinatol 2020. Oct 6. Doi: 10.1038/s41372-020-00850-5. PMID 330242259

Other Review Articles:

1. **Eke AC**, Okigbo C. Mechanical methods for induction of labour: RHL commentary (last revised: 1 August 2012). *The WHO Reproductive Health Library*; Geneva: World Health Organization.
2. Okigbo C, **Eke AC**. Behavioral interventions to reduce the transmission of HIV infection among sex workers and their clients in low and middle-income countries: RHL commentary (1 February 2013). *The WHO Reproductive Health Library*; Geneva: World Health Organization.
3. **Eke AC**, Patterson K. In pregnant women undergoing fetal well-being assessment on admission to the labor ward, is there randomized controlled trial evidence to support the use of fetal vibroacoustic stimulation, biophysical profile assessment, Doppler scanning of the umbilical artery, or sonographic assessment of the amniotic fluid index. *Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, June* 2013. DOI: 10.1002/cca.17.
4. **Eke AC**, Patterson K. In low risk pregnant women undergoing fetal well-being assessment on admission to the labor ward, is there randomized controlled trial evidence to support the use of cardiotocography instead of intermittent auscultation of the fetal heart rate? *Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, June* 2013. DOI: 10.1002/cca.16.
5. **Eke AC**, Patterson K. In women who are in the third stage of labor, which treatment is most effective at improving outcomes? Active or expectant management? *Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, April* 2013. DOI: 10.1002/cca.15.
6. **Eke AC**, Patterson K, Tort S. Is there randomized controlled trial evidence to support the use of calcium channel blockers to inhibit preterm labor? *Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, August* 2013. DOI: 10.1002/cca.176.
7. **Eke AC**, Tort S, Patterson K. Is there randomized controlled trial evidence to support the use of betamimetics for maintenance therapy after threatened preterm labor? *Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, October* 2013. DOI: 10.1002/cca.177.
8. Ezebialu IU, **Eke AC.** Knowledge and practice of emergency contraception among female undergraduates in South Eastern Nigeria. *Ann Med Health Sci Res, 2013*, 3(4); 541-45.

9. **Eke AC**, Patterson K, Tort S. Is there randomized controlled trial evidence to support the use of betamimetics for inhibiting preterm labor? *Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, October 2013*. DOI: 10.1002/cca.178.
10. **Eke AC**, Tort S, Patterson K. Do prophylactic oral betamimetics reduce preterm birth and improve other outcomes in women with a twin pregnancy? *Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, October* 2013. DOI: 10.1002/cca.179/.
11. **Eke AC**, Tort S, Patterson K. Do prophylactic betamimetics given to women with a singleton pregnancy at risk of preterm delivery improve outcomes? *Cochrane Clinical Answers, Cochrane Database of Systematic Reviews, October* 2013. DOI: 10.1002/cca.180.
12. Okigbo CC, **Eke AC**. Skilled Birth Attendance in Nigeria: A Function of Frequency and Content of Antenatal Care. Afr J Reprod Health. 2015; 19(1):25-33.

Case Reports:

1. Ukah CO, Ikpeze OC, Eleje GU, **Eke AC**. Adult granulosa cell tumor associated with endometrial carcinoma: a case report. *J Med Case Rep*. 2011; 5(1): 340. Cited in PubMed; PMID: 21810262.
2. Woo JY, Tate L, Roth S, **Eke AC.** Silent Spontaneous Uterine Rupture at 36 Weeks of Gestation. 2015: Case Rep Obstet Gynecol. 2015. 596826. doi: 10.1155/2015/596826.

Book Chapters, Monographs:

1. 2009
   Chapter Title: Management of Eclampsia and Malaria in Pregnancy
   Book Title: *Protocol for management of common Obstetric emergencies*
   Author List: **Ahizechukwu Eke**, Ikechebelu JI, Ikpeze OC, Adinma JIB, Udigwe G. (2009)
   Published By: Afrihub Publishers
   Editors: John CT, Okpani M.

2. 2018
   Chapter Title: Admission to Labor and Delivery
   Book Title: *Evidence Based Labor and Delivery Management*
   Author List: **Ahizechukwu Eke**, MD MPH
   Published By: JayPee Brothers, 2018
   Editors: Amanda Roman, Vincenzo Berghella.

Other Media [OM] (Videos, Websites, Blogs, Social Media, etc.):

1. Cochrane series

I have dedicated the last 12 years to developing my research skills, which I have used to initiate positive change in individuals back in Africa and here in the US. For the past 11 years, I have been involved with authoring and reviewing several Cochrane systematic reviews and meta-analysis. I write the Obstetric Cochrane Clinical Answer series for the Collaboration, where I served as Associate Editor in Obstetrics. Here are links to my Cochrane clinical answer series:
https://www.cochranelibrary.com/cca/doi/10.1002/cca.241/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.976/related-content
https://www.cochranelibrary.com/cca/doi/10.1002/cca.1851/related-content
https://www.cochranelibrary.com/cca/doi/10.1002/cca.98/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.1905/full

https://www.cochranelibrary.com/cca/doi/10.1002/cca.177/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.1185/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.721/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.1052/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.1051/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.521/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.308/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.134/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.166/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.149/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.173/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.180/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.1637/full
https://www.cochranelibrary.com/cca/doi/10.1002/cca.1185/full

2. Johns Hopkins Medicine Video Series (Breast Cancer in Pregnancy)

I was involved in managing a patient with breast cancer in pregnancy, which ended very well, and got the attention of the Johns Hopkins media. This short video clip was made – and has had over 4,900 views.
https://www.youtube.com/watch?v=aUD7wS5fSUo

FUNDING

EXTRAMURAL Funding:

i. Research Extramural Funding

Study: 2032 IMPAACT Network Direct Costs: (10% salary support)

08/2020 – Current
Pharmacokinetic Properties of Antiretroviral, Anti-tuberculosis, Contraceptive, and Related Drugs During Pregnancy and Postpartum
Role: Lead Investigator for the Cabotegravir arm (Protocol Chair: Mark Mirochnick)

- Goal: to characterize the pharmacokinetics and pharmacodynamics of long active carbotegravir in pregnant women receiving cabotegravir for pre-exposure prophylaxis as part of standard care in a clinical trial.

Study: 1026S/2026 IMPAACT Network Direct Costs: (5% salary support)

11/2019 – Current
Pharmacokinetics and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the United States.
Role: Lead Obstetrics Investigator (Protocol Chair: Mark Mirochnick)

- Goal: prospective phase I study of remdesivir in pregnant and non-pregnant women of childbearing age with COVID-19, to characterize the pharmacokinetics and pharmacodynamics of remdesivir as part of standard care.

Center for AIDS Research (CFAR) HIV Research Grant Total cost: ($50,000)

12/2019 – Current
Rational use of drugs during pregnancy: Tenofovir Alafenamide (TAF) pharmacokinetics and adherence benchmarks in pregnancy and postpartum.
Role: Principal Investigator (PI)

- Goal: To determine the PK of TAF in Plasma and PBMC's of women living with HIV during pregnancy, and to determine TAF adherence benchmarks in pregnancy, and apply the TAF adherence instrument in each trimester of pregnancy and postpartum.

American College of Obstetricians & Gynecologists (ACOG) Warren Pearse Grant Total cost: ($10,000)

06/2019 – Current
Maternal Levels of care: A comprehensive catalogue of regional policies and practices for risk appropriate maternal care in the United States.
Role: Principal Investigator (PI) of several Health Policy initiatives to improve maternal and child care

- Goal: To characterize levels of maternal care, and create a comprehensive catalogue of regional policies and practices for risk-appropriate maternal care in the United States.

UM1 AI069465 (Gupta and Flexner) 12/01/20-11/30/27
0.6 calendar
NIH/NIAID $2,950,074
Johns Hopkins University Baltimore – India Clinical Trials Unit (JHUBI CTU).
Role: Co-Investigator

- Goal: The proposed Clinical Trials Unit will join the most active HIV clinical research sites in Baltimore, Pune, and Chennai, India, to optimize patient-oriented research and to access key populations affected by this epidemic for participation in clinical trials.

Womens Health Reproductive Research (WRHR) (Eke) 07/27/2020-09/22/2020
9.0 calendar
NIH/NICHD $158,993/year
Pharmacometrics of Antiretrovirals in Pregnant Women Living with HIV.
Role: Principal Investigator (PI)

- Goal: Major goal is to advance our knowledge of the pharmacometrics of HIV drugs in pregnant and post-partum women using tools such as physiologically based pharmacokinetic (PBPK) modeling and population pharmacokinetic modeling (POPPK).

K23HD104517 (Eke) 09/23/2020-80/30/2025
9.0 calendar
NIH/NICHD $158,993/year
Understanding Medication Safety and Pharmacometrics of novel and Antiretrovirals in Pregnant Women Living with HIV.
Role: Principal Investigator (PI)

- Goal: Major goal is to advance our knowledge of the pharmacology and safety of several new HIV drugs in pregnant and post-partum women, using innovative tools, such as pharmacometrics and physiologically based pharmacokinetic (PBPK) modeling.

ii. Educational Extramural Funding

National Institute of Health (NIH) T-32 Grant (Grant # 2T32GM06691-16). Total Cost: $57,000 (annually)

6/2017 – 6/2019
National Institute of Health (NIH) T-32 Training Grant in Clinical Pharmacology and Molecular Sciences
Principal Investigators (Craig Hendrix; Kelly Dooley).
Role: Trainee in Clinical Pharmacology and Maternal Fetal Medicine

- Goal: This program is designed to train highly-qualified physicians and pharmacists to become independent clinical investigators applying the tools of clinical pharmacology to advance drugs from the laboratory to the clinical treatment and prevention of disease in pregnant women. This program addresses a critical shortage of well-trained clinician-scientists who conduct hands-on studies in humans, particularly in the area of clinical pharmacology.

iii. Clinical Extramural Funding

Johns Hopkins Alliance for a Healthier World Clinical Grant Total Cost: $25,000

6/2017 – 6/30/2018
Strengthening Health Service Delivery and Building Human Capacity to Reduce Maternal Morbidity and Mortality in Sierra Leone
Principal Investigator (Jean Anderson).
Role: Maternal Fetal Medicine Co-Investigator

- Goal: In Sierra Leone, the probability of a woman age 15-49 dying from maternal causes is 58% as compared to 1% in the United States. The lack of women's reproductive health providers and inadequate levels of basic and comprehensive obstetric care are major factors affecting increased maternal mortality and morbidity, as well as the loss of workforce suffered during the 2014 Ebola crisis. To address these gaps, the project developed a phased, comprehensive, sustainable, and high-quality strategy to build capacity in women's reproductive health care. The team drew on science and expertise from business process improvement and total quality management (TQM), and bioengineering design and techniques to rethink healthcare service capacity with a focus on equity and justice.

CLINICAL ACTIVITIES

Certification:

Medical, other state/government licensure:

6/15/2012 – 6/30/2013	Missouri Practicing Medical License (License # 2012015941)
7/1/2013 – 6/30/2016	Michigan Practicing Medical License (License # L283447)
7/1/2016 – Current	Maryland Practicing Medical License (License # D0080760)

Boards, other specialty certification:

2010 - Educational Commission for Foreign Medical Graduates (ECFMG)
2012 – Current - Basic Life Support (BLS)
2012 – Current - Advanced Trauma Life Support (ACLS)
2012 - Fellow, West African College of Surgeons (FWACS)
2014 - Fellow, International College of Surgeons (FICS)
2018 - Fellow, American College of Obstetrics and Gynecology (FACOG)
2020 - Diplomate, American College of Clinical Pharmacology (DACCP)

Clinical (Service) Responsibilities:

7/2019 – Present
Assistant Professor in Maternal Fetal Medicine, Johns Hopkins University, Maryland, United States

- High risk obstetric care of pregnant women with diverse and chronic medical conditions during pregnancy, including chronic hypertension, pre-eclampsia, diabetes, cardiac disease, kidney and liver transplants, chronic renal diseases, preconception consultations and other medical issues.
- Provide care, treatment and advice for acute health conditions for patients on labor and delivery, including serving as the back-up MFM for the Generalist Obstetricians and Gynecologists.
- Round on very high risk antepartum patients during my antepartum grounds when serving as the antepartum attending of the week.
- Perform complicated and difficult surgeries on pregnant patients, including cervical cerclages, repeat cesarean sections, myomectomies during pregnancy, peripartum hysterectomies, and other surgical complications
- Perform and read routine as well as complicated ultrasound scans of pregnant women during pregnancy
- Perform antenatal procedures, including but not limited to amniocentesis and chorionic villus sampling on pregnant patients.

EDUCATIONAL ACTIVITIES

Mentoring

Pre-doctoral Advisees /Mentees:

5/12/2016 **Tina Chaalan, MD**, 3rd year Obstetrics & Gynecology resident, St Joes hospital, Ann Arbor, MI. Under my direction and help with mentoring in research, Tina received her MD degree from Michigan State University in 2016.
Eke AC, Chaalan T, Shukr G, Eleje GU, Okafor CI. A systematic review and meta-analysis of progestogen use for maintenance tocolysis after preterm labor in women with intact membranes. *Int J Gynec Obstet*, 2016, 132(1): 11-16.
Eke AC, Chaalan TT, Shukr GH, Nashif SK, Eleje GU. Intra-abdominal saline irrigation at cesarean section: a systematic review and meta-analysis. *J Matern Fet Neonatal Med*, 2015; 14:1-7.

5/12/2016 **Ghadear Shukr, MD**, 3rd year Obstetrics & Gynecology resident, Henry Ford Hospital, Detroit, MI. Under my direction and help with mentoring in research, Ghadear received her MD degree from Michigan State University in 2016.

Eke AC, Chaalan T, Shukr G, Eleje GU, Okafor CI. A systematic review and meta-analysis of progestogen use for maintenance tocolysis after preterm labor in women with intact membranes. *Int J Gynec Obstet*, 2016, 132(1): 11-16.
Eke AC, Chaalan TT, Shukr GH, Nashif SK, Eleje GU. Intra-abdominal saline irrigation at cesarean section: a systematic review and meta-analysis. *J Matern Fet Neonatal Med*, 2015; 14:1-7.

5/12/2016 **Sereen Nashif, MD**, 3rd year Obstetrics & Gynecology resident, Loyola University, Maywood, IL. Under my direction and help with mentoring in research, Sereen received her MD degree from Michigan State University in 2016.
Eke AC, Chaalan TT, Shukr GH, Nashif SK, Eleje GU. Intra-abdominal saline irrigation at cesarean section: a systematic review and meta-analysis. *J Matern Fet Neonatal Med*, 2015; 14:1-7.

9/1/18 **Katie Lichter, MPH**, 3rd year medical student, Loyola Stritch Medical School, Chicago. Under my direction and help with mentoring in research, Katie received her master's degree in Public Health from the Johns Hopkins University School of Public Health.
Lichter KE, Sheffield J, Graham EM, **Eke AC**. Adjuvant 17-hydroxyprogesterone caproate in women with ultrasound indicated cerclage: a systematic review and meta-analysis. *J Matern Fetal Neonatal Med.* 2019 Jan 24: 1-8. Doi: 10. 1080/14767058.2019. 1568406. [Epub ahead of print]. PMID 30626240.

Post-doctoral Advisees /Mentees:

2/5/17 **Elizabeth Oler, MD**, 4th year obstetric and gynecology resident, Johns Hopkins University School of Medicine, Baltimore, MD. Under my direction and help with mentoring in research, Elizabeth completed a research entitled "Meta-analysis of randomized controlled trials comparing 17-alpha-hydroxyprogesterone caproate to vaginal progesterone for prevention of recurrent spontaneous preterm birth". This paper was presented as a poster presentation at the Society for Maternal Fetal Medicine (SMFM) conference in 2017, and published in the International Journal of Gynecology and Obstetrics in 2017 - Oler E, **Eke AC**, Hesson A. Meta-analysis of randomized controlled trials comparing 17-alpha-hydroxyprogesterone caproate to vaginal progesterone for prevention of recurrent spontaneous preterm birth. *Int J Gynaecol Obs 2017*; 138(1): 12-16. PMID: 28369874.

11/17/17 **Ikechukwu Mbachu, MBBS**, 4th year obstetric and gynecology resident, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria. Under my direction and help with mentoring in research, Ikechukwu completed a research entitled "Effect of on-site training on the accuracy of blood loss estimation in a simulated obstetrics environment". This paper was presented as an oral presentation at the Society of Gynecologists and Obstetricians of Nigeria (SOGON) conference in 2017, and published in the International Journal of Gynecology and Obstetrics in 2017 - Mbachu II, Udigwe GO, Ezeama Co, Eleje GU, ***Eke AC***. Effect of on-site training on the accuracy of blood loss estimation in a simulated obstetrics environment. *Int J Gynaecol Obstet*. 2017; 138(1):12-16. PMID: 28236647.

3/2/19 **Katelyn Uribe, MD**, 4th year obstetric and gynecology resident, Johns Hopkins University School of Medicine, Baltimore, MD. Under my direction and help with mentoring in research, Katelyn completed a research entitled "Laterality of single umbilical arteries and associated anomalies". This paper was presented as an oral in the 2019 ACOG National Conference in Nashville, Tennessee.

5/1/20 **Matt Thimm, MD**, 2nd year obstetric and gynecology resident, Johns Hopkins University School of Medicine, Baltimore, MD. Under my direction and help with mentoring in research, Matt is currently conducting a retrospective chart review of pregnant women who used tenofovir disoproxil fumarate (TDF) and those who used tenofovir alafenamide (TAF) during pregnancy.

2/20/20 **Matthew Miller, MD**, 1st year Maternal Fetal Medicine Fellow, Johns Hopkins University School of Medicine, Baltimore, MD. Under my direction and help with mentoring in research, Matt is currently conducting a retrospective chart review of pregnant women who used antihypertensives – Procardia during pregnancy. Our aim is to conduct a randomized controlled trial, looking at once daily dosing versus twice daily dosing in pregnant women using Procardia for blood pressure control during pregnancy.

3/11/20 **Nicole Gavin, MD**, 2nd year Maternal Fetal Medicine Fellow, Johns Hopkins University School of Medicine, Baltimore, MD. Under my direction and help with mentoring in research, Nicole is currently conducting a retrospective chart review of pregnant women focused on ultrasound abnormalities (specifically fetal abdominal wall defects). This will be her thesis presentation.

11/15/19 **Juliet Bishop, MD**, 3nd year Maternal Fetal Medicine/Genetics Fellow, Johns Hopkins University School of Medicine, Baltimore, MD. Under my direction and help with mentoring in research, Jewels completed a retrospective chart review of doppler abnormalities in pregnant women with Downs Syndrome. This was her thesis presentation.

RESEARCH ACTIVITIES

Research:

My research interests involve a comprehensive understanding of methods for improving the safety and effective use of therapeutic drugs in women during pregnancy and lactation. I have been involved in managing pregnant patients with a prior history of preterm birth in the setting of HIV-AIDS since 2005, and have dedicated the last 12 years of my career developing my clinical and research skills in the care of HIV patients in pregnancy, which I have used to develop and design a number of cesarean section clinical trials in Obstetrics & Maternal-Fetal Medicine. My academic training and research experience to date have provided me with an excellent background in Obstetrics, and specifically in preterm birth management, including systematic reviews and cost effectiveness analysis. I write the Obstetric Cochrane Clinical Answer series for the Collaboration, where I serve as Associate Editor in Obstetrics. I was the 1st author of one of the Cochrane systematic reviews that changed practice in the management of HIV transmission in sero-discordant couples– *Sperm washing to prevent HIV transmission from HIV-infected men but allowing conception in sero-discordant couples,* published in Cochrane Database of Systematic Reviews. 2011 ;(1):CD008498. doi: 10.1002/14651858.CD008498.pub2.

My short term career ambition as a Maternal Fetal Medicine specialist/Obstetrician include (1) identifying and investing in clinical, research and educational programs that enhance the quality of life of pregnant patients with preterm birth and HIV; (2) understanding, refining and improving methods of drug use in pregnancy through continuous process improvement and performance measures; (3) understanding the pharmacokinetics and pharmacodynamics of drug use in pregnancy; (4) ensuring the safe and effective use of medications during pregnancy by planning and prevention through preconception care; (5) developing a comprehensive human resource strategy for implementing Obstetric-Fetal Pharmacology Research Unit (OPRU) Network programs in pregnancy; and (5) ultimately promoting and facilitating safe and effective use

of medications in pregnancy. My long term career ambition is to sustain my involvement in women's health by combining my experience in Clinical Pharmacology, Maternal/Fetal Medicine & Obstetrics and Gynecology to develop multidisciplinary approaches to investigate the mechanisms of drug disposition and response in pregnancy.

ORGANIZATIONAL ACTIVITIES

Editorial Activities:

2/2018 - Present Associate Editor, Journal of Maternal Health, Neonatology & Perinatology
https://mhnpjournal.biomedcentral.com/about/editorial-board

7/2020 - Present Associate Editor, Obstetrics and Gynecology (Green Journal)
https://journals.lww.com/greenjournal/pages/editorialboard.aspx

Editorial Board appointments:

2/2018 - Present Board member, Journal of Maternal Health, Neonatology & Perinatology
https://mhnpjournal.biomedcentral.com/about/editorial-board

7/2020 - Present Board member, Obstetrics and Gynecology (Green Journal)
https://journals.lww.com/greenjournal/pages/editorialboard.aspx

Journal peer review activities:

Peer reviewer, Obstetrics & Gynecology (Green Journal)
Peer reviewer, International Journal of Gynecology and Obstetrics (IJGO)
Peer reviewer, American Journal of Perinatology (AJP)
Peer reviewer, PLOS One
Peer reviewer, British Journal of Gynecology and Obstetrics (BJOG)
Peer reviewer, Australian and New Zealand Journal of Gynecology and Obstetrics (ANZJOG)
Peer reviewer, Acta Obstetricia et Gynecologica Scandinavica (AOGS)
Peer reviewer, African Review of Obstetrics and Gynecology (AROG)
Peer reviewer, BMC Infectious Diseases
Peer reviewer, Nigerian Journal of Clinical Practice (NJCP)
Peer reviewer, European Journal of Obstetrics, Gynecology and Reproductive Biology (EJOGRB)
Peer reviewer, Journal of Adolescent Health (JAH)
Peer reviewer, Afrimedic Journal of Medicine, Nigeria (AJMN)
Peer reviewer, Annals of Obstetrics and Gynecology of Nigeria (AOGN)
Peer reviewer, Clinical Pharmacokinetics
Peer reviewer, American Journal of Clinical Pharmacology (ACCP)
Peer reviewer, American Journal of Perinatology

Advisory Committees, Review Groups/Study Sections:

10/2016 -10/2018 - ACOG Committee Member, American Congress of Obstetricians and Gynecologists Junior Fellow Congress Advisory Council (JFCAC): Committee involved with making governing decisions for the junior fellows of the American Congress of Obstetricians and Gynecologists (ACOG).

1/2017 - 6/2019 - SMFM Committee Member, Society for Maternal Fetal Medicine (SMFM) Health Policy Committee): Committee to review and enact all Society for Maternal Fetal Medicine Health Policy concerns, including publication of national health policy documents.

3/2019 - 4/2020 - ACOG National Committee Member, ACOG National Genetics Committee: Committee in charge of authoring and reviewing all ACOG related Genetics publications.

4/2019 - Present - ACOG National Committee Member, ACOG National Obstetrics Practice Bulletins Committee: Committee in charge of authoring and reviewing all ACOG practice bulletins related to Obstetrics.

5/2019 - Present - FDA Advisory Committee Member, 17 alpha hydroxyprogesterone caproate use for the prevention of preterm birth: Committee in charge of reviewing and making recommendations to the FDA about the use of 17 alpha hydroxyprogesterone caproate, especially in the setting of the 2 phase IV RCT's that showed dissimilar results.

Professional Societies:

2002 – Date: Member, International Leadership Association
2003 – Date: Member, Nigerian Medical Association
2009 – Date: Trainee, Royal College of Obstetricians and Gynecologists
2010 – Date: Member, National Post-graduate College of OBGYN
2011 – Date: Member, American Public Health Association
2012 – Date: Fellow, West African Post-graduate College of OBGYN
2012 – Date: Member, American Medical Association
2012 – Date: Member, American Congress of Obstetricians and Gynecologists
2013 – Date: Member, Reproductive Health Research, World Health Organization
2016 – Date: Associate Member, Society for Maternal Fetal Medicine
2017 – Date: Member, American College of Clinical Pharmacology
2018 – Date: Fellow, American College of Obstetricians and Gynecologists
2017 – Date: Member, American Society for Clinical Pharmacology and Therapeutics

Professional Leadership Activities:

10/2004 – 10/2005 - Past President, Public Health Club, National Youths Service Corps, Akwa Ibom State, Nigeria
6/2006 – 7/2007 - Obstetrics Quality Assurance Member, Nnamdi Azikiwe University Teaching Hospital, Nnewi.
6/2009 – 6/2010 - Academic Chief Resident, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria
5/2009 – 5/2010 - Vice Chair, Junior Fellows of the Society of Obstetricians and Gynecologists, South Eastern Nigeria
9/2010 – 5/2011 - Vice President, Minority Students Association, Harvard School of Public Health, Boston Massachusetts
10/2013 - 10/2014 - American College of Obstetricians & Gynecologists (ACOG) Vice Chair, Junior Fellows, Michigan Section of the American College of Obstetricians and Gynecologists
10/2014 - 10/2015 - American College of Obstetricians & Gynecologists (ACOG) Chair, Junior Fellows, Michigan Section of the American College of Obstetricians and Gynecologists
10/2015 - 10/2016 - American College of Obstetricians & Gynecologists (ACOG) Junior Fellow Secretary/Treasurer for District V, American College of Obstetricians and Gynecologists
10/2015 - 10/2016 - American College of Obstetricians & Gynecologists (ACOG) ***District*** V Junior Fellow Representative to the American Medical Association (AMA) Residents and Fellows Section (RFS)

10/2016 - 10/2017 - American College of Obstetricians & Gynecologists (ACOG) Junior Fellow Vice Chair for District IV, American College of Obstetricians and Gynecologists
10/2017 - 10/2018 - American College of Obstetricians & Gynecologists (ACOG) Junior Fellow Chair for District IV, American College of Obstetricians and Gynecologists
10/2018 – 9/2019 - American College of Obstetricians & Gynecologists (ACOG) Junior Fellow Immediate Past Chair for District IV, American College of Obstetricians and Gynecologists
8/2020 - Present - American College of Obstetricians & Gynecologists (ACOG) Maryland Section Vice Chair.

RECOGNITION

Awards, Honors:

2006 - Association of Resident Doctors (ARD) award for outstanding and consistent contribution to leadership
2007 - Essay winner, Global Forum for Health Research/Lancet International Essay Competition, 2007
2008 - Society of Gynecologists and Obstetricians of Nigeria (SOGON) outstanding resident doctor's award for decisive contributions to women's health
2011 - A.G. Leventis Scholarship Award for Academic Excellence, Harvard School of Public Health
2011 - Nominated for the Albert Schweitzer Award, the highest accolade for students graduating from the HSPH
2012 - HIVMA Travel Scholarship Award, 2012 to the World's AIDS Conference, Washington DC.
2012 - Diversity Minority Fellowship Award, Barnes Jewish Hospital, St Louis
2013 - Winning oral presentation, ACOG Junior fellow District V Resident research day, Louisville Kentucky
2014 - American Medical Association (AMA) Foundation National Excellence in Medicine Leadership Award for outstanding leadership skills
2014 - Overall highest CREOG Score, 2014 in-training examinations, Michigan State University/Sparrow Hospital
2014 - Inductee, Alpha Omega Alpha (AOA) Honor Medical Society, Michigan State University
2015 - National Institute of Health (NIH)/National Medical Association Scholar
2015 - Ephraim McDowell Award for best Junior Fellow research paper in ACOG District V
2015 - Society for Maternal Fetal Medicine (SMFM) Resident Award for Excellence in Obstetrics
2015 - Society for Maternal Fetal Medicine (SMFM) Quilligan Scholar
2015 - American Congress of Obstetricians and Gynecologists (ACOG) Junior Fellow Rising Star in Advocacy National Award
2015 - Michigan State University Outstanding Award for Best Medical Student/Resident Educator
2015 - Overall highest CREOG Score, 2015 in-training examinations, Michigan State University/Sparrow Hospital
2016 - American Congress of Obstetricians and Gynecologists (ACOG) Donald Richardson's Paper Prize National Award
2016 - Michigan State University Outstanding Award for Best Medical Student/Resident Educator
2017 – Cochrane Kenneth Warren Prize for best high quality methodological review, Cochrane Collaboration
2017 – Paul Leitman's Global Health Fellowship Travel Award, Johns Hopkins University School of Medicine
2017 - Society for Reproductive Investigation (SRI) award for Best New Investigator poster presentation
2019 – Society for Reproductive Investigation (SRI) Pfizer Presidential Award
2019 – American College of Obstetrics & Gynecology (ACOG) Warren Pearse Health Policy Award
2019 – Center for AIDS Research (CFAR) Faculty Development Award.
2020 – Distinguished Teaching Society (DTS) of the Johns Hopkins University School of Medicine Award.

Invited Talks:

JHMI/Regional

11/3/2017 Johns Hopkins University, Department of Gynecology and Obstetrics Joint Pediatrics and Maternal Fetal Medicine Conference. Baltimore, MD. "*Management of Intrauterine Growth Restriction."*

11/7/2017 Johns Hopkins University, Department of Gynecology and Obstetrics Journal Club. "*Vaginal Progesterone in the management of the short cervix in singleton pregnancies."*

12/8/2017 Johns Hopkins University, Department of Gynecology and Obstetrics Joint Pediatrics and Maternal Fetal Medicine Conference. Baltimore, MD. "*Differential diagnosis of thoracic lesions on ultrasound."*

6/9/2018 Johns Hopkins University, Department of Clinical Pharmacology weekly Conference. Baltimore, MD. *"Pharmacologic Research In Pregnant Women, It is time to get it right."*

11/3/2018 Johns Hopkins University, Department of Gynecology and Obstetrics Joint Pediatrics and Maternal Fetal Medicine Conference. Baltimore, MD. "*Congenital Diaphragmatic Hernia: Current trends and management."*

1/11/2019 Greater Baltimore Medical Center, Department of Gynecology and Obstetrics Grand Rounds. "*Preventing the first cesarean section*".

1/24/2019 Johns Hopkins University, Department of Gynecology and Obstetrics Grand Rounds. "*2 Years of Obstetrics & Gynecology Fellowship: What I've learned*".

National

7/12/2013 Sparrow Hospital/Michigan State University Department of Gynecology and Obstetrics Morbidity and Mortality Conference. Lansing, MI. *"Failed surgical abortion in a patient with distorting leiomyoma."*

7/17/2013 Sparrow Hospital/Michigan State University Department of Gynecology and Obstetrics Morbidity and Mortality Conference. Lansing, MI. *"Outpatient management of presumed spontaneous abortion requiring emergency laparoscopy for ruptured ectopic pregnancy.*

8/16/2013 Sparrow Hospital/Michigan State University Department of Gynecology and Obstetrics Grand Rounds Speaker on "*Use of anti-mullerian hormone to design ovarian stimulation"*.

2/13/2014 Sparrow Hospital/Michigan State University Department of Gynecology and Obstetrics Grand Rounds presentation: *"Leiomyosarcoma – Bogeyman or Real Threat?"*

5/11/2014 Michigan State University College of Medicine - Speaker on "*Power Point Presentations"* Dean's Teaching Fellowship Session.

8/4/2014 Sparrow Hospital/Michigan State University Department of Gynecology and Obstetrics Morbidity and Mortality Conference. *"Emergent cesarean delivery for loss of fetal cardiac activity in the setting of maternal respiratory distress."*

5/6/2015 Sparrow Hospital/Michigan State University Department of Gynecology and Obstetrics Morbidity and Mortality Conference.. *"Michigan Maternal and Infant Health: Presentation of Research and Discussion of Next Steps."*

11/12/2019 George Washington University, Department of Obstetrics and Gynecology Grand Rounds. "*17 alpha hydroxyprogesterone caproate (17 OHPC) use for the prevention of spontaneous preterm birth: how did we get here?*".

12/24/2019 Michigan State University, Department of Obstetrics and Gynecology Grand Rounds. "The FDA, AMAG, and *17 alpha hydroxyprogesterone caproate (17 OHPC) use for the prevention of spontaneous preterm birth?*".

10/15/2020 American College of Obstetrics & Gynecology (ACOG) Michigan Section. "*17 alpha hydroxyprogesterone caproate (17 OHPC) use for the prevention of spontaneous preterm birth – What we should be doing*"

10/31/2020 American College of Obstetrics & Gynecology (ACOG) Debate. "*Is it so long PROLONG – Do we, or don't we? Is there still a role for 17-OHPC?*"

International

3/2014 Course Director and Instructor, two-week seminar on prevention of maternal mortality. Federal Medical Center, Umuahia, Abia State, Nigeria.

3/2015 Course Instructor, 1 day course on gynecologic ultrasound during pregnancy. University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria.

4/2016 Course Instructor, 1 day course on obstetric ultrasound. University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria.

4/2017 Course Instructor, 3 day course on obstetric ultrasound during pregnancy. Nnamdi Azikiwe University Teaching Hospital, Nigeria..

4/2018 Course Instructor, 3 day course on obstetric ultrasound during pregnancy. Nnamdi Azikiwe University Teaching Hospital, Nigeria.

7/2019 Course Instructor, 2 day course on obstetric ultrasound during pregnancy. Nnamdi Azikiwe University Teaching Hospital, Nigeria.

OTHER PROFESSIONAL ACCOMPLISHMENTS

Posters:

1. Bishop J, Jones A, Johnson C, **Eke AC**, Jelin A, Blakemore K. *What antenatal fetal surveillance parameters predict fetal demise in Down's Syndrome?*. Poster Presented at the Society for Maternal Fetal Medicine 38th annual Conference (SMFM), Dallas, TX, February 2020.
2. **Eke AC**, Sheffield JS, Graham E. *Adjuvant 17-hydroxyprogesterone caproate in women with history-indicated cerclage: A cost effectiveness and decision analysis*. Poster Presented at the Society for Maternal Fetal Medicine 37th annual Conference (SMFM), Las Vegas, NV, February 2019.
3. **Eke AC**, Northington F, Everett A, Dhananjay D, McClarin L, Graham E. *The relationship between histologic-chorioamnionitis and biomarkers to identify neonates at increased risk of brain injury*. Poster Presented at the Society for Maternal Fetal Medicine 37th annual Conference (SMFM), Las Vegas, NV, February 2019.
4. **Eke AC**, Northington F, Everett A, Dhananjay D, McClarin L, Graham E. *Identification of intrauterine growth restriction (IUGR) via biomarkers in cord blood and neonatal serum*. Poster Presented at the Society for Maternal Fetal Medicine 37th annual Conference (SMFM), Las Vegas, NV, February 2019.
5. **Eke AC**, Northington F, Everett A, Dhananjay D, McClarin L, Graham E. *The relationship between maternal preeclampsia and neonatal blood biomarkers*. Poster Presented at the Society for Maternal Fetal Medicine 37th annual Conference (SMFM), Las Vegas, NV, February 2019.

6. Handal-Orefice, **Eke AC.** *Trends in congenital fetal cardiac anomalies and delivery at high volume centers*. Poster Presented at the Society for Maternal Fetal Medicine 37th annual Conference (SMFM), Las Vegas, NV, February 2019.
7. **Eke AC,** Dooley K. Sheffield J. *Integrase inhibitor versus protease inhibitor (PI) – based antiretroviral therapy (ART) in late pregnancy and rapid HIV viral load reduction in ART naïve patients: Cost effectiveness analysis*. Poster Presented at the Society for Maternal Fetal Medicine 38th annual Conference (SMFM), Dallas, TX, February 2018
8. **Eke AC,** Graham E, Sheffield J. *A cost effectiveness and decision analysis of reverse syphilis testing compared to traditional testing in pregnancy for diagnosis of syphilis in pregnancy in high burden regions;* Poster presented at the Society for Reproductive Investigation (SRI) 64th annual conference, Orlando, Florida, March 2017.
9. **Eke AC,** Sfakianaki A, Hesson A. *Impact of delivery route on neonatal morbidity and mortality in isolated gastroschisis: a systematic review and meta-analysis;* Poster presented at the Society for Reproductive Investigation (SRI) 64th annual conference, Orlando, Florida, March 2017.
10. **Eke AC,** Onasanya D, Johnson C. *Vaginal progesterone: cost and health care utilization for preventing preterm births in the United States;* Poster to be presented at the American Congress of Obstetricians and Gynecologists (ACOG) annual conference, San Diego, CA in May 2017.
11. Oler E, **Eke AC**, Hesson A. *17 alpha hydroxyprogesterone compared to vaginal progesterone for prevention of recurrent spontaneous preterm birth in singleton gestations*. Poster Presentation at the Society for Maternal Fetal Medicine 37th annual Conference (SMFM), Las Vegas, NV, January 2017.
12. Albino N, Johnson C, **Eke AC**, Szymanski L. *Retrospective analysis of delivery methods for breech singleton 22-26 6/7 week gestation*. Poster Presented at the Society for Maternal Fetal Medicine 37th annual Conference (SMFM), Las Vegas, NV, January 2017.
13. **Eke, AC,** Buras AL, Drnec SE, Woo JY. *Vaginal progesterone versus cervical cerclage for the prevention of preterm births in women with a short cervix*; Poster presented at the 35th Society for Maternal Fetal Medicine Conference (SMFM), San Diego, 2015.
14. **Eke AC,** Ecchoffo JB. *Glyburide versus Metformin for the management of Gestational Diabetes Mellitus; a decision and cost effectiveness analysis*. Poster presented at the 2014 ACOG Annual General Meeting (AGM), Chicago, Illinois. May 2014.
15. **Eke AC**, Xia Y, Eke UA, Eleje GU. *Hepatitis B immunoglobulin during pregnancy for the prevention of mother to child transmission of hepatitis B virus*. Poster Presentation at the Society for Maternal Fetal Medicine 34th annual Conference (SMFM), New Orleans, LA, February 2014.
16. **Eke, AC**, Enumah AP, Akabuike JC (2012 July), *HIV/AIDS Associated Stigma in South-Eastern Nigeria: A Community Based Study.* Poster presented at the International AIDS Conference in Washington DC, July, 2012.
17. **Eke AC**, Mbamara S, Eleje G, Okonkwo J, Udigwe G, Ugboaja J, Oguejiofor C, Mbachu I. (2009, October). *Ectopic pregnancy in Nnewi, Nigeria: A 5 year study at a tertiary health care institution*. Poster presented at: 19th World Congress of Obstetricians and Gynecologists (FIGO); Cape Town, South Africa.
18. **Eke AC,** Akabuike JC, Oragwu C. (2011, April). *Measuring Maternal Mortality: Improving Data Collection for Maternal Deaths in Nigeria*. Poster presented at: Unite for Sight/Global Health International Conference; New Haven, CT.
19. **Eke, A**, Eleje G, Ijeneme U. (2009, October). *Presentation and outcome of eclampsia at the Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria – a 10 year review*. Poster presented at: 19th World Congress of Obstetricians and Gynecologists (FIGO); New Haven, South Africa.

20. **Eke, A**, Eleje G, Ijeneme U. (2009, October). *Uterine rupture in a Nigerian teaching hospital.* Poster presented at: 19th World Congress of Obstetricians and Gynecologists (FIGO); Cape Town, South Africa.
21. **Eke AC,** Ecchoffo JB (September 2013). *Insulin pumps compared with Lantus/Novolog for the management of diabetes in pregnancy; a cost effectiveness analysis and decision analysis.* Oral presentation at the ACOG Junior fellow District V Resident research day, Louisville Kentucky, September 2013.
22. **Eke AC.** (2007, October). *Debating how to do Cesarean sections in developing countries*. Oral Presentation presented at: West African College of Surgeons (WACS) forum; Lagos, Nigeria.
23. **Eke AC**. (2008, November). *The Challenges of the Obstetrician in a developing country*. Oral Presentation presented at: Association of Resident Doctors (ARD) Annual General Meeting (AGM); Abuja, South Africa.
24. **Eke AC.** (2008, December). *Incomplete miscarriages at Nnamdi Azikiwe University Teaching Hospital, Nnewi*. Oral Presentation presented at: Post-Abortion Care Network (PACNET); Nnewi, Nigeria.
25. **Eke AC.** (2007, October). *Impediments to health-care research in developing countries*. Oral Presentation presented at: Nigerian Medical Association, Nnewi branch Annual General Meeting (AGM), Nnewi, Nigeria.
26. **Eke AC**, Chavarro JE, Harris HR, Missmer SA. (2011, September). *Vitamin A and endometriosis risk: A prospective cohort study*. Oral Presentation presented at: 11th World Congress on Endometriosis; Montpellier, France.
27. **Eke, A**, Eleje G. (2009, October). *Abruptio placentae – A 5 year study at the Nnamdi Azikiwe University Teaching Hospital, Nnewi, Nigeria*. Oral Presentation presented at: 19th World Congress of Obstetricians and Gynecologists (FIGO); Cape Town, South Africa.
28. **Eke, A,** Eleje G. (2009, October). *Molar pregnancies in a Nigerian Teaching Hospital*. Oral Presentation presented at: 19th World Congress of Obstetricians and Gynecologists (FIGO); Cape Town, South Africa.
29. **Eke, A,** Eleje G. (2009, October). *The pregnancy outcome in elderly primigravida – A 5 year study*. Oral Presentation presented at: 19th World Congress of Obstetricians and Gynecologists (FIGO); Cape Town, South Africa.
30. **Eke, A**, Eleje G, Okonkwo J, Udigwe G, Ugboaja J. (2009, October). *Presentation and pattern of infertility in a Nigerian tertiary hospital*. Oral Presentation presented at: 19th World Congress of Obstetricians and Gynecologists (FIGO); Cape Town, South Africa.
31. **Eke, A,** Eleje GU, Ijeneme UN. (2009, October). *Ovarian carcinoma in a Nigerian Teaching Hospital*. Oral Presentation presented at: 19th World Congress of Obstetricians and Gynecologists (FIGO); Cape Town, South Africa.

Oral/Podium Presentations:

1. **Eke AC**, Northington F, Everett A, Dhananjay D, McClarin L, Graham E. *Neonatal blood biomarkers associated with absent or reversed end diastolic flow (AREDF).* **Oral paper** presented at the Society for Maternal Fetal Medicine 37th annual Conference (SMFM), Las Vegas, NV, February 2019.
2. **Eke AC**, Northington F, Everett A, Dhananjay D, McClarin L, Graham E. *The relationship between histologic-funisitis and biomarkers to identify neonates at increased risk of brain injury*. **Oral paper** presented at the Society for Reproductive Investigation (SRI) 66th annual Conference, Paris, France, March 2019.

Community Services:

09/2013 - 10/2015

ACOG Michigan Junior Fellow Chair, MI, United States

Overseeing all ACOG junior fellow OB/GYN resident activities in Michigan, including advocacy, junior fellow community service projects, junior fellow research activities, junior fellow tool kits, and working together with the Michigan Infant Health Program (MIHP) to provide home support and promote healthy pregnancies, good birth outcomes, and healthy infants. I have significantly increased resident involvement in health promotion in the State of Michigan. My programs are very well received by the community and have benefited many citizens. There is an increasing number of women coming in for OB/GYN screening & annual exams due to our activities here in Michigan. I represented the Michigan Section of ACOG at the Michigan House of Senate during the Michigan ACOG legislative day in 05/2014, defending the breast density bill. The Michigan section of ACOG had many concerns with this bill, including creating unnecessary fear in patients and the lack of evidence around offering any other screening tests.

03/2014 - 06/2016

ACOG Rising Star in Advocacy, MI, United States

I have been involved in promoting an advocacy project, the Eliminate Breast Cancer Advocacy Program (EBCAP). The goals of EBCAP is to encourage grass-root advocacy for elimination of breast cancer by increasing breast health and breast cancer awareness through culturally and linguistically appropriate education and outreach for women in communities in Michigan. My advocacy efforts include creating culturally and linguistically appropriate breast health educational materials and promoting breast cancer screenings through educational workshops. As part of my breast cancer advocacy efforts, I represented the Michigan Section of ACOG at the Michigan House of Senate during the 1st Michigan ACOG legislative day on 05/08/2014. I was recently awarded the Junior Fellow rising star in advocacy award for 2014.

07/2014 - 06/2017

ACOG/American Medical Association, MI, United States

ACOG District V Junior Fellow Representative to the American Medical Association (AMA),
I was recently elected to serve as ACOG District V Junior Fellow Representative to the American Medical Association (AMA) Residents and Fellows Section (RFS). My roles include advising District V residents and fellows on the policy-making, educational programs and electioneering process of the American Medical Association. Current projects being addressed by the AMA that affect ACOG include physician workforce shortage, approaches to GME funding, breast density notification, genetic testing restrictions based on specialty and the role of bariatric surgery as part of the essential benefits plan. I recently started working on educating residents, fellows and junior attendings on the impact of the Physician Payment Sunshine Act(PPSA) which took effect on 9/30/14. This AMA/ACOG role has given me the opportunity to work with residents in other parts of the country on several AMA legislative health policy bills.